

FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE (MODIFIED)

ATTORNEY'S DOCKET NUMBER

X-12420

**TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371**

U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.5)

10/018037INTERNATIONAL APPLICATION NO.
PCT/US00/16319INTERNATIONAL FILING DATE
11 July 2000 (11.07.00)PRIORITY DATE CLAIMED
19 July 1999 (19.07.99)TITLE OF INVENTION: **sPLA₂ INHIBITORS**APPLICANT(S) FOR DO/EO/US: **Ho-Shen Lin and Michael Enrico Richett**

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ has been transmitted by the International Bureau.
 - c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☒ A copy of the International Preliminary Examination Report (IPER), including any annexes, and, if not in English, an English language translation of the annexes to the IPER under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A **FIRST** preliminary amendment.
14. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

JE07 Rec'd PCT/PTO 11 DEC 2001

U.S. APPLICATION NO. (if known, see 37 CFR 1.52) <div style="font-size: 1.5em; font-weight: bold;">10/018037</div>		INTERNATIONAL APPLICATION NO. <div style="font-weight: bold;">PCT/US00/16319</div>		ATTORNEY'S DOCKET NUMBER <div style="font-weight: bold;">X-12420</div>	
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17. <input checked="" type="checkbox"/> The following fees are submitted: <div style="margin-left: 20px;"> BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. \$1040.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$890.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... \$740.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$710.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) \$100.00 </div> <div style="text-align: right; margin-top: 10px;"> ENTER APPROPRIATE BASIC FEE AMOUNT = \$ 890.00 </div> <table border="1" style="width:100%; border-collapse: collapse; margin-top: 5px;"> <tr> <td colspan="4">Surcharge of \$130.00 for furnishing the oath or declaration later than <u> 20 </u> <u> 30 </u> months from the earliest claimed priority date (37 CFR 1.492(e)).</td> <td style="width:10%; text-align: right;">\$</td> <td style="width:10%;"></td> </tr> <tr> <td style="width:20%; text-align: center;">CLAIMS</td> <td style="width:20%; text-align: center;">NUMBER FILED</td> <td style="width:20%; text-align: center;">NUMBER EXTRA</td> <td style="width:20%; text-align: center;">RATE</td> <td style="width:10%; text-align: right;">\$</td> <td style="width:10%;"></td> </tr> <tr> <td>Total claims</td> <td style="text-align: center;">27 -20=</td> <td style="text-align: center;">7</td> <td style="text-align: right;">X \$18.00</td> <td style="text-align: right;">\$</td> <td style="text-align: right;">126.00</td> </tr> <tr> <td>Independent claims</td> <td style="text-align: center;">3 - 3=</td> <td style="text-align: center;">0</td> <td style="text-align: right;">X \$84.00</td> <td style="text-align: right;">\$</td> <td></td> </tr> <tr> <td colspan="4">MULTIPLE DEPENDENT CLAIM(S) (if applicable)</td> <td style="text-align: right;">+ \$280.00</td> <td style="text-align: right;">\$</td> </tr> <tr> <td colspan="4" style="text-align: right;">TOTAL OF ABOVE CALCULATIONS =</td> <td style="text-align: right;">\$</td> <td style="text-align: right;">126.00</td> </tr> <tr> <td colspan="4">Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).</td> <td style="text-align: right;">\$</td> <td></td> </tr> <tr> <td colspan="4" style="text-align: right;">SUBTOTAL =</td> <td style="text-align: right;">\$</td> <td style="text-align: right;">1,016.00</td> </tr> <tr> <td colspan="4">Processing fee of \$130.00 for furnishing English translation later than <u> 20 </u> <u> 30 </u> months from the earliest claimed priority date (37 CFR 1.492(f)).</td> <td style="text-align: right;">\$</td> <td></td> </tr> <tr> <td colspan="4" style="text-align: right;">TOTAL NATIONAL FEE =</td> <td style="text-align: right;">\$</td> <td style="text-align: right;">1,016.00</td> </tr> <tr> <td colspan="4">Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property</td> <td style="text-align: right;">\$</td> <td></td> </tr> <tr> <td colspan="4" style="text-align: right;">TOTAL FEES ENCLOSED =</td> <td style="text-align: right;">\$</td> <td style="text-align: right;">1,016.00</td> </tr> <tr> <td colspan="4"></td> <td style="text-align: right;">Amount to be refunded</td> <td style="text-align: right;">\$</td> </tr> <tr> <td colspan="4"></td> <td style="text-align: right;">charged</td> <td style="text-align: right;">\$</td> </tr> </table>	Surcharge of \$130.00 for furnishing the oath or declaration later than <u> 20 </u> <u> 30 </u> months from the earliest claimed priority date (37 CFR 1.492(e)).				\$		CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	\$		Total claims	27 -20=	7	X \$18.00	\$	126.00	Independent claims	3 - 3=	0	X \$84.00	\$		MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ \$280.00	\$	TOTAL OF ABOVE CALCULATIONS =				\$	126.00	Reduction by 1/2 for filing by small entity, if applicable. 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a.	<input type="checkbox"/>	A check in the amount of \$ _____ to cover the above fees is enclosed.
b.	<input checked="" type="checkbox"/>	Please charge my Deposit Account No. 05-0840 in the amount of <u>\$ 1,016.00</u> to cover the above fees. A duplicate copy of this sheet is enclosed.
c.	<input checked="" type="checkbox"/>	The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 05-0840. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
ELI LILLY AND COMPANY
 PATENT DIVISION/1104
 LILLY CORPORATE CENTER
 INDIANAPOLIS, INDIANA 46285

December 5, 2001 **25885**

PATENT TRADEMARK OFFICE

Francis O. Ginah

 SIGNATURE

Francis O. Ginah

 NAME

44.712
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REGISTRATION NUMBER
TELEPHONE NUMBER

13-06-2001
X-12420

00944673.3(11-07-2000) - US00/16319(11-07-2000)

P'DESCPAMD

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Novel sPLA₂ Inhibitors

Field of the Invention

This invention relates to novel indole compounds
5 useful for Inflammatory Diseases.

Background of the Invention

The structure and physical properties of human non-
pancreatic secretory phospholipase A₂ (hereinafter
10 called, "sPLA₂") has been thoroughly described in two
articles, namely, "Cloning and Recombinant Expression of
Phospholipase A₂ Present in Rheumatoid Arthritic
Synovial Fluid" by Seilhamer, Jeffrey J.; Pruzanski,
Waldemar; Vadas Peter; Plant, Shelley; Miller, Judy A.;
15 Kloss, Jean; and Johnson, Lorin K.; The Journal of
Biological Chemistry, Vol. 264, No. 10, Issue of April
5, pp. 5335-5338, 1989; and "Structure and Properties of
a Human Non-pancreatic Phospholipase A₂" by Kramer, Ruth
M.; Hession, Catherine; Johansen, Berit; Hayes,
20 Gretchen; McGray, Paula; Chow, E. Pingchang; Tizard,
Richard; and Pepinsky, R. Blake; The Journal of
Biological Chemistry, Vol. 264, No. 10, Issue of April
5, pp. 5768-5775, 1989; the disclosures of which are
incorporated herein by reference.

25

-2-

It is believed that sPLA₂ is a rate limiting enzyme in the arachidonic acid cascade which hydrolyzes membrane phospholipids. Thus, it is important to develop compounds which inhibit sPLA₂ mediated release of fatty acids (e.g., arachidonic acid). Such compounds would be of value in general treatment of conditions induced and/or maintained by overproduction of sPLA₂; such as sepsis or rheumatoid arthritis.

It is desirable to develop new compounds and treatments for sPLA₂ induced diseases.

Summary of the Invention

This invention provides novel indole compounds having potent and selective effectiveness as inhibitors of mammalian sPLA₂.

This invention is also the use of novel indole compounds useful in the treatment and prevention of Inflammatory Diseases.

This invention is also the use of novel of indole compounds to inhibit mammalian sPLA₂ mediated release of fatty acids.

25

-3-

This invention is also a pharmaceutical composition containing any of the indole compounds of the invention.

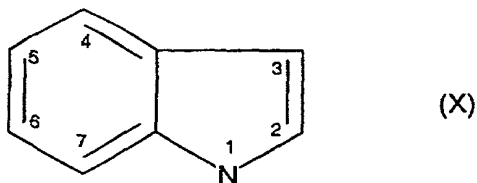
5 **I. Definitions:**

 The term, "Inflammatory Diseases" refers to diseases such as inflammatory bowel disease, sepsis, septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic
10 fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy,
15 enterapathric spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infectious arthritis, gonococcal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease,
20 arthritis associated with "vasculitic syndromes", polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris, pseudo gout, non-articular rheumatism,
25 bursitis, tenosynovitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing).

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miscellaneous forms of arthritis, neuropathic joint
disease (charco and joint), hemarthrosis (hemarthrosic),
Henoch-Schonlein Purpura, hypertrophic osteoarthropathy,
multicentric reticulohistiocytosis, arthritis associated
5 with certain diseases, surcoilosis, hemochromatosis,
sickle cell disease and other hemoglobinopathries,
hyperlipoproteineimia, hypogammaglobulinemia,
hyperparathyroidism, acromegaly, familial Mediterranean
fever, Behat's Disease, systemic lupus erythrematosis,
10 or relapsing polychondritis and related diseases which
comprises administering to a mammal in need of such
treatment a therapeutically effective amount of the
compound of formula I in an amount sufficient to inhibit
sPLA₂ mediated release of fatty acid and to thereby
15 inhibit or prevent the arachidonic acid cascade and its
deleterious products.

The term, "indole nucleus" refers to a nucleus
(having numbered positions) with the structural
20 formula (X):



The indole compounds of the invention employ
certain defining terms as follows:

-5-

The term, "alkyl" by itself or as part of another substituent means, unless otherwise defined, a straight or branched chain monovalent hydrocarbon radical such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tertiary
5 butyl, sec-butyl, n-pentyl, and n-hexyl.

The term, "alkenyl" employed alone or in combination with other terms means a straight chain or branched monovalent hydrocarbon group having the stated
10 number range of carbon atoms, and typified by groups such as vinyl, propenyl, crotonyl, isopentenyl, and various butenyl isomers.

The term, "hydrocarbyl" means an organic group
15 containing only carbon and hydrogen.

The term, "halo" means fluoro, chloro, bromo, or iodo. The term, heterocyclic radical, refers to radicals derived from monocyclic or polycyclic, saturated or
20 unsaturated, substituted or unsubstituted heterocyclic nuclei having 5 to 14 ring atoms and containing from 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen or sulfur. Typical heterocyclic radicals are pyrrolyl, pyrrolodiny, piperidiny, furanyl,
25 thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl,

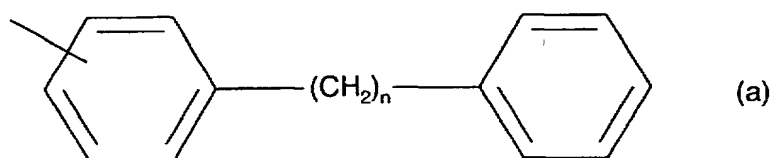
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indolyl, carbazolyl, norharmanyl, azaindolyl,
benzofuranyl, dibenzofuranyl, dibenzothiophenyl,
indazolyl, imidazo(1,2-A)pyridinyl, benzotriazolyl,
anthranilyl, 1,2-benzisoxazolyl, benzoxazolyl,
5 benzothiazolyl, purinyl, pyridinyl, dipyridyl,
phenylpyridinyl, benzylpyridinyl, pyrimidinyl,
phenylpyrimidinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl,
phthalazinyl, quinazolinyl, morpholino, thiomorpholino,
homopiperazinyl, tetrahydrofuranyl, tetrahydropyranyl,
10 oxacanyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl,
tetrahydrothiophenyl, pentamethylenesulfadyl, 1,3-
dithianyl, 1,4-dithianyl, 1,4-thioxanyl, azetidyl,
hexamethyleneiminium, heptamethyleneiminium, piperazinyl
and quinoxaliny.

15

The term, "carbocyclic radical" refers to radicals
derived from a saturated or unsaturated, substituted or
unsubstituted 5 to 14 membered organic nucleus whose ring
forming atoms (other than hydrogen) are solely carbon
20 atoms. Typical carbocyclic radicals are cycloalkyl,
cycloalkenyl, phenyl, spiro[5.5]undecanyl, naphthyl,
norbornanyl, bicycloheptadienyl, tolulyl, xylenyl,
indenyl, stilbenyl, terphenyl, diphenylethylenyl,
phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl,
25 biphenyl, bibenzyl and related bibenzyl homologues
represented by the formula (a):

-7-



where n is a number from 1 to 8.

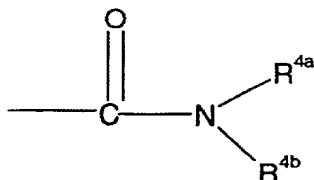
- 5 The term, "non-interfering substituent", refers to radicals suitable for substitution at positions 4,5,6 and/or 7 of the indole nucleus and on other nucleus substituents (as hereinafter described for Formula I), and radicals suitable for substitution on the
- 10 heterocyclic radical and carbocyclic radical as defined above. Illustrative non-interfering radicals are C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C₁-C₈ alkoxy, C₂-C₈
- 15 alkenyloxy, C₂-C₈ alkynyloxy, C₂-C₁₂ alkoxyalkyl, C₂-C₁₂ alkoxyalkyloxy, C₂-C₁₂ alkylcarbonyl, C₂-C₁₂ alkylcarbonylamino, C₂-C₁₂ alkoxyamino, C₂-C₁₂ alkoxyaminocarbonyl, C₁-C₁₂ alkylamino, C₁-C₆ alkylthio, C₂-C₁₂ alkylthiocarbonyl, C₁-C₈ alkylsulfinyl, C₁-C₈
- 20 alkylsulfonyl, C₂-C₈ haloalkoxy, C₁-C₈ haloalkylsulfonyl, C₂-C₈ haloalkyl, C₁-C₈ hydroxyalkyl, -C(O)O(C₁-C₈ alkyl), -(CH₂)_n-O-(C₁-C₈ alkyl), benzyloxy, phenoxy, phenylthio, -(CONHSO₂R), -CHO, amino, amidino,

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bromo, carbamyl, carboxyl, carbalkoxy, $-(CH_2)_n-CO_2H$,
chloro, cyano, cyanoguanidiny, fluoro, guanidino,
hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino,
iodo, nitro, phosphono, $-SO_3H$, thioacetal, thiocarbonyl,
5 and carbonyl; where n is from 1 to 8 and R is C_1-C_8
alkyl.

The term, "organic substituent" refers to a
monovalent radical consisting of carbon and hydrogen
10 with or without oxygen, nitrogen, sulfur, halogen, or
other elements. Illustrative organic substituents are
 C_1-C_8 alkyl, aryl, C_7-C_{14} aralkyl, C_7-C_{14} alkaryl, C_3-C_8
cycloalkyl, C_1-C_8 alkoxyalkyl and these groups
substitued with halogen, $-CF_3$, $-OH$, C_1-C_8 alkyl, amino,
15 carbonyl, and $-CN$.

The term, "acylamino acid group" is represented by
the formula:



20

wherein R^{4a} is selected from the group consisting of H,
(C_1-C_6)alkyl, (C_1-C_6)alkoxy, heteroaryl and aryl, $-CF_3$;
and wherein NR^{4b} is an amino acid residue with the

-9-

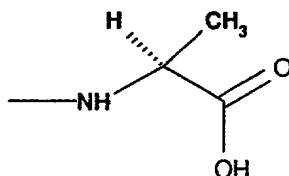
nitrogen atom being part of the amino group of the amino acid. A typical amino acid is selected from the group comprising isoleucine, valine, phenylalanine, aspartic acid, leucine, glycine, asparagine, cystein, glutamine, glutamic acid, histidine, lysine, methionine, serine, threonine, tryptophan, tyrosine and derivatives thereof. Also contemplated within the definition of amino acid is l-proline, d-proline and derivatives thereof. Also contemplated within the definition of amino acids are peptides, polypeptides and derivatives thereof.

The term "substituted group" is an organic group substituted with one or more non-interfering substituents.

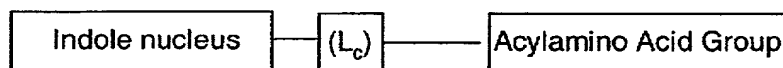
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The terms, "amino acid residue" refer to the portion of the amino acid group coupled at the nitrogen atom of the amino terminus. It is the amino acid less a hydrogen atom from the amino terminus. It is further illustrated as used herein for the amino acid alanine attached at the nitrogen atom as shown below:

-10-

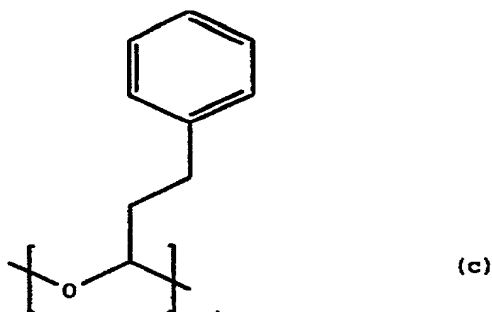
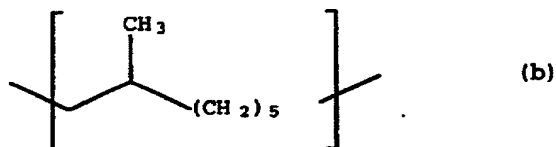
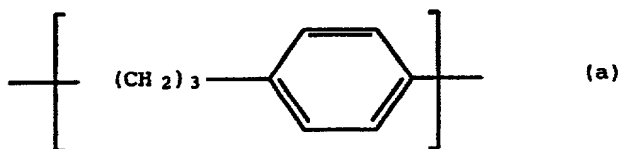


The words, "acylamino acid linker" refer to a divalent linking group symbolized as, $-(L_C)-$, which has the function of joining the 4 - position of the indole nucleus to an acylamino acid group in the general relationship:



The words, "acylamino acid linker length", refer to the number of atoms (excluding hydrogen) in the shortest chain of the linking group $-(L_C)-$ that connects the 4 - position of the indole nucleus with the acylamino acid group. The presence of a carbocyclic ring in $-(L_C)-$ counts as the number of atoms approximately equivalent to the calculated diameter of the carbocyclic ring. Thus, a benzene or cyclohexane ring in the acid linker counts as 2 atoms in calculating the length of $-(L_C)-$. Illustrative acylamino acid linker groups are;

-11-



wherein, groups (a), (b) and (c) have acid linker lengths of 5, 7, and 2, respectively.

5

The term, "(acidic group)" means an organic group which when attached to an indole nucleus at position 5, through suitable linking atoms (hereinafter defined as the "acid linker"), acts as a proton donor capable of hydrogen bonding. Illustrative of an (acidic group) are the following:

-5-tetrazolyl,

-SO₃H,

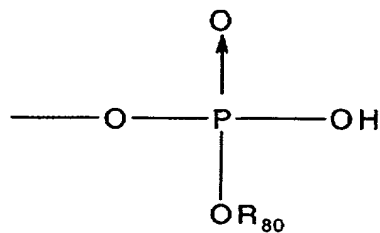
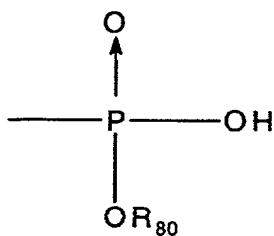
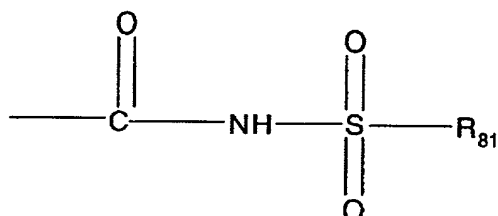
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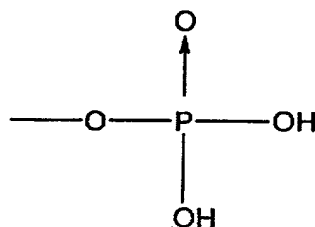
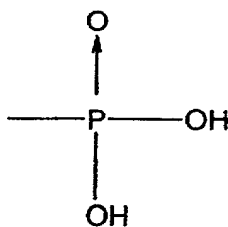
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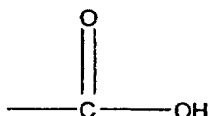
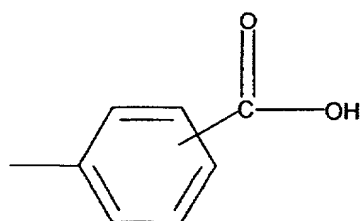
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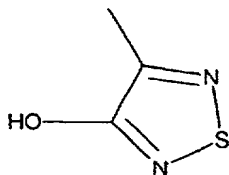
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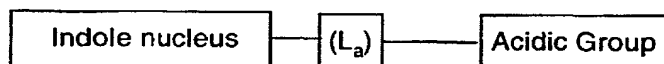


or



where n is 1 to 8, R₈₀ is a metal or C₁-C₈ and R₈₁
 5 is an organic substituent or -CF₃.

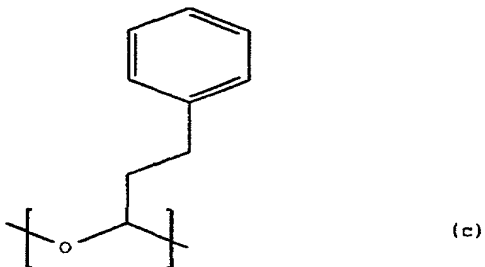
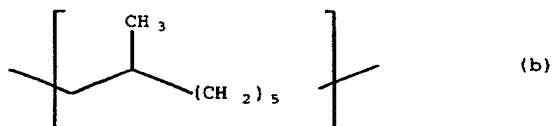
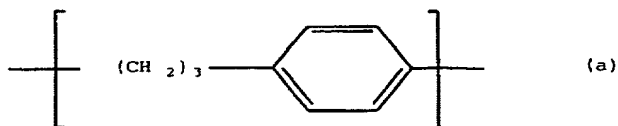
The words, "acid linker" refer to a divalent
 linking group symbolized as, -(L_a)-, which has the
 function of joining the 5 position of the indole nucleus
 10 to an acidic group in the general relationship:



The words, "acid linker length", refer to the number
 of atoms (excluding hydrogen) in the shortest chain of the
 15 linking group -(L_a)- that connects the 5 position of the

-14-

indole nucleus with the acidic group. The presence of a carbocyclic ring in $-(L_a)-$ counts as the number of atoms approximately equivalent to the calculated diameter of the carbocyclic ring. Thus, a benzene or cyclohexane ring in
 5 the acid linker counts as 2 atoms in calculating the length of $-(L_a)-$. Illustrative acid linker groups are;



10 wherein, groups (a), (b), and (c) have acid linker lengths of 5, 7, and 2, respectively.

The term, "amine", includes primary, secondary and tertiary amines.

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The terms, "mammal" and "mammalian" include human and domesticated quadrupeds.

The term, "alkylene chain of 1 or 2 carbon atoms" refers to the divalent radicals, $-\text{CH}_2\text{-CH}_2-$ and $-\text{CH}_2-$.

5

The term, "group containing 1 to 4 non-hydrogen atoms" refers to relatively small groups which form substituents at the 2 position of the indole nucleus, said groups may contain non-hydrogen atoms alone, or non-hydrogen atoms plus hydrogen atoms as required to satisfy the unsubstituted valence of the non-hydrogen atoms, for example; (i) groups absent hydrogen which contain no more than 4 non-hydrogen atoms such as $-\text{CF}_3$, $-\text{Cl}$, $-\text{Br}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{SO}_3$; and (ii) groups having hydrogen atoms which contain less than 4 non-hydrogen atoms such as $-\text{CH}_3$, $-\text{C}_2\text{H}_5$, and $-\text{CH=CH}_2$.

10
15

The term "oxime amide" means the radical,
 $-\text{C=NOR-C(O)NH}_2$

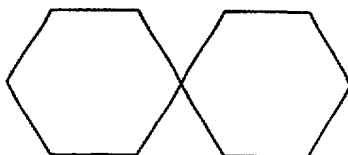
20

The term "thio-oxime amide" means the radical
 $-\text{C=NOR-C(S)-NH}_2$.

The term "spiro[5.5]undecanyl" refers to the group
represented by the formula;

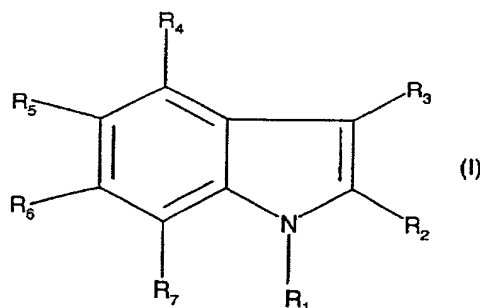
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-16-



II. The amino acid 1H-indole Compounds of the Invention:

The present invention provides novel classes of
5 indole compounds useful as sPLA2 inhibitors for the
treatment of inflammation. Classes of indole compounds
of this invention include indole glyoxylamide amino acid
derivatives, indole-3-oxime amide amino acid derivatives
and indole acetamide amino acid derivatives. The
10 compounds of the invention have the general formula (I)
or a pharmaceutically acceptable salt, solvate or
prodrug thereof;



15

wherein ;

R₁ is selected from groups (a), (b), and (c)

wherein;

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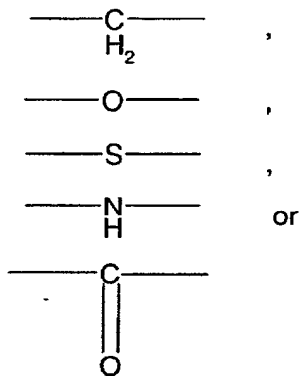
(a) is C7-C20 alkyl, C7-C20 haloalkyl, C7-C20 alkenyl, C7-C20 alkynyl, carbocyclic radical, or heterocyclic radical, or

(b) is a member of (a) substituted with one or
 5 more independently selected non-interfering substituents; or

(c) is the group $-(L_1)-R_{11}$; where, $-(L_1)-$ is a divalent linking group of 1 to 8 atoms and where R_{11} is a group selected from (a) or (b);

10 R_2 is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

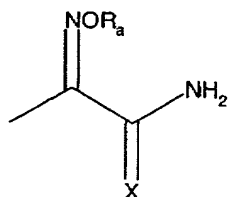
R_3 is $-(L_3)-Z$, where $-(L_3)-$ is a divalent linker group selected from a bond or a divalent group selected from:



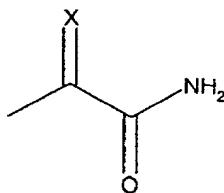
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and Z is selected from an oxime amide or oxime thioamide group represented by the formulae,

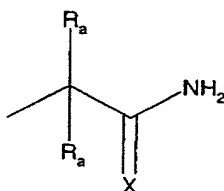
-18-



or



or



5

wherein X is oxygen or sulfur, R_a is independently selected from hydrogen, C_1 - C_8 alkyl, aryl, C_1 - C_8 alkaryl, C_1 - C_8 alkoxy, aralkyl and -CN;

R_4 is the group, $-(L_C)-(acylamino\ acid\ group)$;

10 wherein $-(L_C)-$, is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

R_5 is selected from hydrogen, a non-interfering substituent, or the group, $-(L_a)-(acidic\ group)$; wherein $-(L_a)-$, is an acid linker having an acid linker length

15 of 1 to 8.

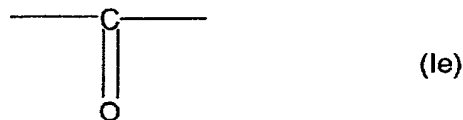
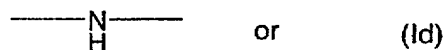
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R₆ and R₇ are selected from hydrogen, non-interfering substituent, carbocyclic radical, carbocyclic radical substituted with non-interfering substituent(s), heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

Preferred Subgroups of Compounds of Formula (I):

Preferred R₁ substituents:

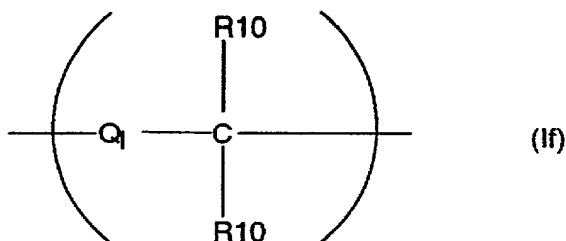
A preferred subclass of compounds of formula (I) are those where for R₁ the divalent linking group -(L₁)- is a group represented by any one of the following formulae (Ia), (Ib), (Ic), (Id), (Ie), or (If):



15

or

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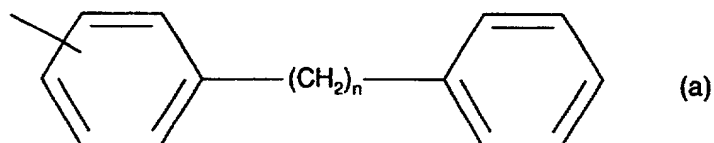
where Q_1 is a bond or any of the divalent groups (Ia),
 (Ib), (Ic), (Id), (Ie), and (If) and each R_{10} is
 5 independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl or
 C_{1-8} alkoxy.

Particularly preferred as the linking group $-(L_1)-$ of
 R_1 is an alkylene chain of 1 or 2 carbon atoms, namely,
 10 $-(CH_2)-$ or $-(CH_2-CH_2)-$.

The preferred group for R_{11} is a substituted or
 unsubstituted group selected from the group consisting of
 C_5-C_{14} cycloalkyl, C_5-C_{14} cycloalkenyl, phenyl, naphthyl,
 15 norbornanyl, bicycloheptadienyl, tolulyl, xylenyl,
 indenyl, stilbenyl, terphenyl, diphenylethylenyl,
 phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl,
 biphenyl, bibenzyl and related bibenzyl homologues
 represented by the formula (a);

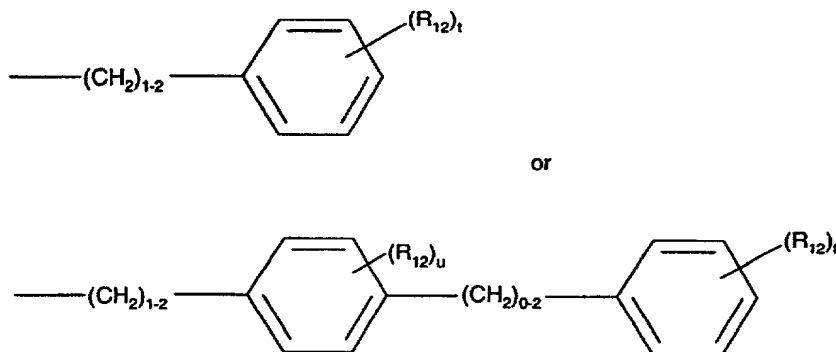
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where n is a number from 1 to 8.

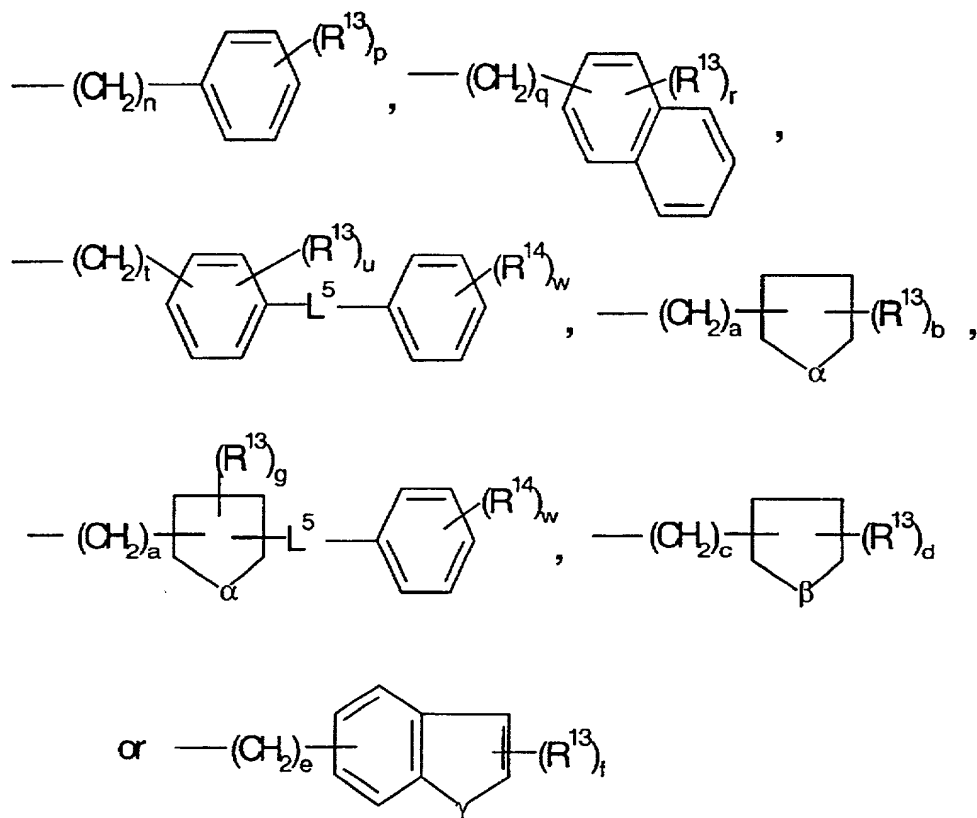
- Particularly preferred are compounds wherein for R_1
 5 the combined group $-(L_1)-R_{11}$ is selected from the group consisting of



- where R_{12} is a radical independently selected from halo,
 C_1-C_8 alkyl, C_1-C_8 alkoxy, $-S-(C_1-C_8 \text{ alkyl})$, $-O-(C_1-C_8$
 10 $\text{alkyl})$ and C_1-C_8 haloalkyl where t is a number from 0 to
 5 and u is a number from 0 to 4 is the group $-(L_1)-R_{11}$;
 where, $-(L_1)-$ is a divalent linking group of 1 to 8
 atoms and where R_{11} is a group selected from (a) or (b).

- 15 Preferred for R_{11} is $-(CH_2)_m-R^{12}$ wherein m is an
 integer from 1 to 6, and R^{12} is (d) a group represented by
 the formula:

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wherein a, c, e, n, q, and t are independently an integer from 0 to 2, R¹³ and R¹⁴ are independently selected from a halogen, C₁ to C₈ alkyl, C₁ to C₈

5 alkyloxy, C₁ to C₈ alkylthio, aryl, heteroaryl, and C₁ to C₈ haloalkyl, α is an oxygen atom or a sulfur atom, L⁵ is a bond, —(CH₂)_v—,

—C=C—, —CC—, —O—, or —S—, v is an integer from 0 to 2, β is —CH₂— or —(CH₂)₂—, γ is an oxygen atom or a sulfur

10 atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer

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from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group consisting of C₁ to C₆ alkyl, C₁ to C₈ alkyloxy, C₁ to C₈ haloalkyloxy, C₁ to C₈ haloalkyl, aryl, and a halogen.

5

Preferred R₂ substituents:

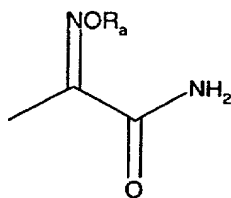
R₂ is preferably selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, -O-(C₁-C₃ alkyl),

10 -S-(C₁-C₃ alkyl), -C₃-C₄ cycloalkyl -CF₃, halo, -NO₂, -CN, -SO₃. Particularly preferred R₂ groups are selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, -CF₃, -Cl, -Br, or -O-CH₃.

15 **Preferred R₃ substituents:**

A preferred subclass of compounds of formula (I) are those wherein X is oxygen.

Another preferred subclass of compounds of
20 formula (I) are those wherein Z is an oxime amide group.



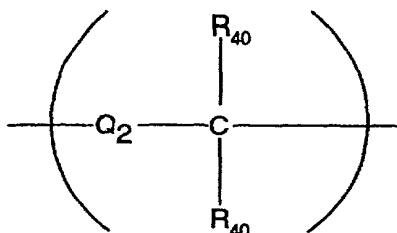
-24-

Also preferred are compounds of formula (I) wherein R_3 is an oxime amide group and R_a is hydrogen, methyl or ethyl. For the group R_3 it is preferred that the linking group $-(L_3)-$ be a bond.

5

Preferred R_4 substituents:

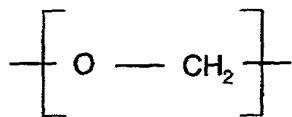
Another preferred subclass of compounds of formula (I) are those wherein R_4 is a substituent having an acylamino acid linker with an acylamino acid linker length of 2 or 3 and the acylamino acid linker group, $-(L_C)-$, for R_4 is selected from a group represented by the formula;



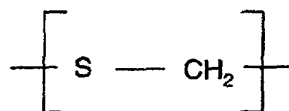
where Q_2 is selected from the group $-(CH_2)-$, $-O-$, $-NH-$, $-C(O)-$, and $-S-$, and each R_{40} is independently selected from hydrogen, C_1 - C_8 alkyl, aryl, C_1 - C_8 alkaryl, C_1 - C_8 alkoxy, aralkyl, and halo. Most preferred are compounds where the acylamino acid linker, $-(L_C)-$, for R_4 is selected from the specific groups;

20

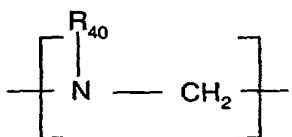
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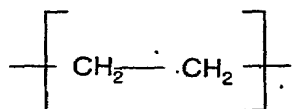
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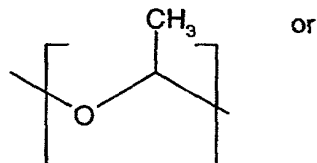
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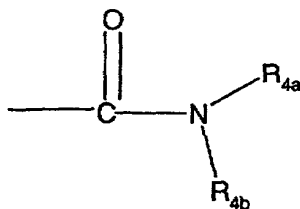


,

where R₄₀ is hydrogen or C₁ -C₈ alkyl.

Preferred as the (acylamino acid group) in the group R₄

5 is the group:



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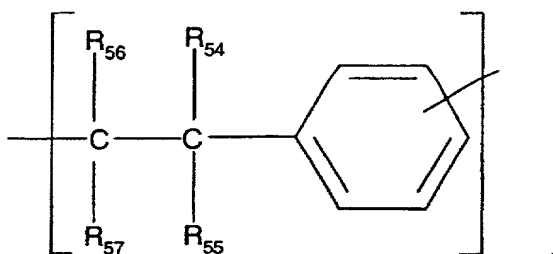
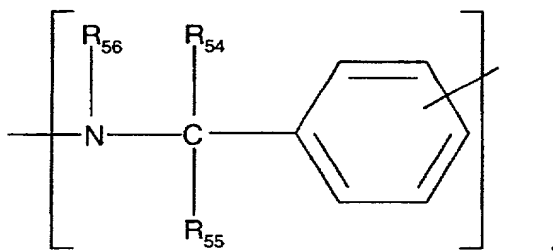
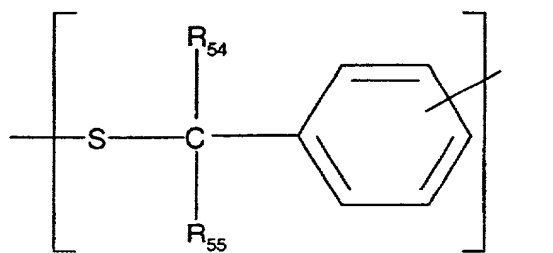
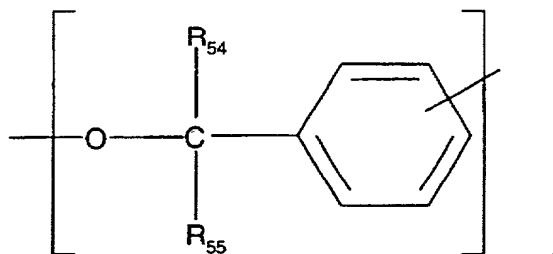
wherein R^{4a} is selected from the group consisting of H,
(C₁-C₆)alkyl, (C₁-C₆)alkoxy, heteroaryl and aryl; and
wherein NR^{4b} is an amino acid residue of either a natural
or unnatural amino acid with the nitrogen atom being part
5 of the amino group of the amino acid. A preferred R^{4a}
group is the group hydrogen (H). A preferred source of
amino acid residue is the amino acid group selected from
the group comprising isoleucine, valine, phenylalanine,
aspartic acid, leucine, glycine and isomers and
10 derivatives thereof. A salt or a prodrug derivative of
the (acylamino acid group) is also a suitable substituent.

Particularly preferred are R^{4b} groups that combine
with the nitrogen atom to represent amino acid residues
15 from the amino acid groups selected from: glycine,
glycine methyl ester, L-alanine, L-alanine methylester,
L-leucine, L-leucine methyl ester, L-aspartic acid, L-
aspartic acid dimethyl ester, L-phenyl alanine, L-
phenylalanine methyl ester, malonic acid, malonic acid
20 dimethylester, L-valine, L-valine methyl ester, L-
isoleucine, L-isoleucine methyl ester, or salt, and
derivatives thereof.

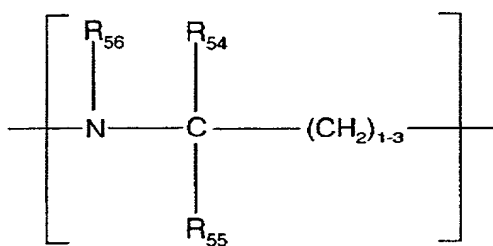
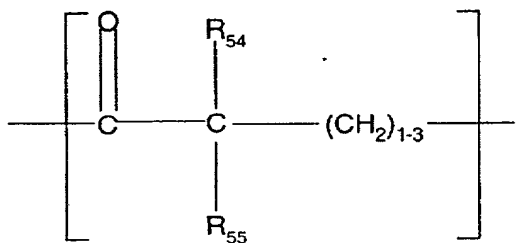
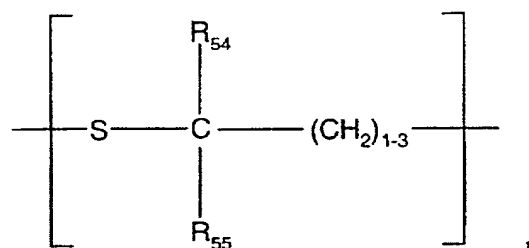
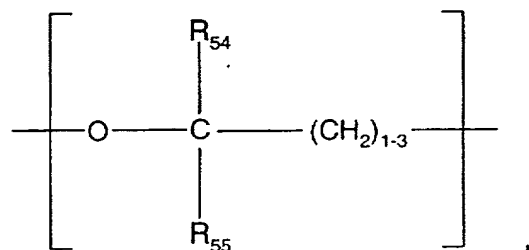
Preferred R₅ Substituents:

25 Preferred acid linker, -(L_a)-, for R₅ is selected from
the group consisting of;

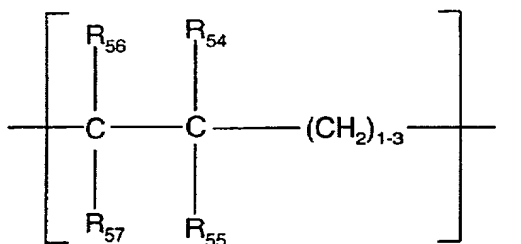
-27-



-28-



and



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wherein R₅₄, R₅₅, R₅₆ and R₅₇ are each independently hydrogen, C₁-C₈ alkyl, C₁-C₈ haloalkyl, aryl, C₁-C₈ alkoxy, or halo. Preferred (acidic group) for R₅ is selected from the group consisting of -CO₂H, -SO₃H and

5 -P(O)(OH)₂.

Preferred R₆ and R₇ substituents:

Another preferred subclass of compounds of formula (I) are those wherein for R₆ and R₇ the non-

10 interfering substituent is independently methyl, ethyl, propyl, isopropyl, thiomethyl, -O-methyl, C₄-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C₁-C₆ alkoxy, C₂-C₆

15 alkenyloxy, C₂-C₆ alkynyloxy, C₂-C₁₂ alkoxyalkyl, C₂-C₁₂ alkoxyalkyloxy, C₂-C₁₂ alkylcarbonyl, C₂-C₁₂ alkylcarbonylamino, C₂-C₁₂ alkoxyamino, C₂-C₁₂ alkoxyaminocarbonyl, C₁-C₁₂ alkylamino, C₁-C₆ alkylthio, C₂-C₁₂ alkylthiocarbonyl, C₁-C₆ alkylsulfinyl, C₁-C₆

20 alkylsulfonyl, C₂-C₆ haloalkoxy, C₁-C₆ haloalkylsulfonyl, C₂-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, -C(O)O(C₁-C₆ alkyl), -(CH₂)_n-O-(C₁-C₆ alkyl), benzyloxy, phenoxy, phenylthio, -(CONHSO₂R), -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -(CH₂)_n-CO₂H,

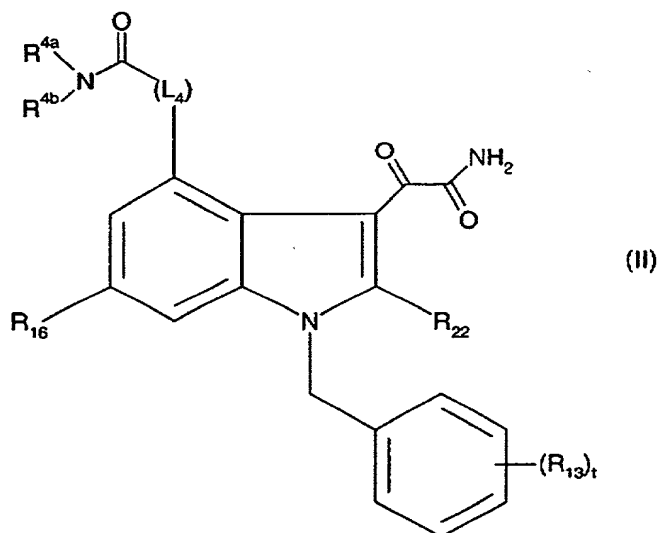
25 chloro, cyano, cyanoguanidiny, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino,

iodo, nitro, phosphono, $-\text{SO}_3\text{H}$, thioacetal, thiocarbonyl, and carbonyl; where n is from 1 to 8.

Most preferred as non-interfering substituents are
5 methyl, ethyl, propyl, and isopropyl.

Preferred compounds of the invention are those having the general formula (II), or a pharmaceutically acceptable salt, solvate or prodrug derivative thereof;

10

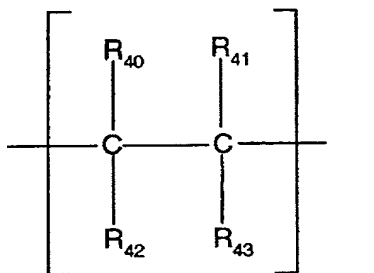
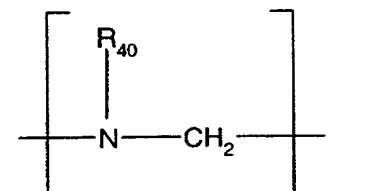
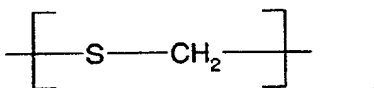
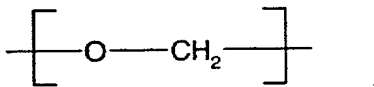


wherein ;

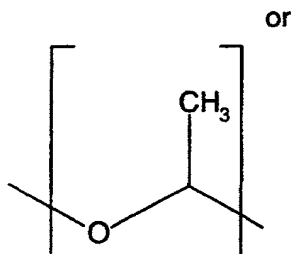
15 R_{22} is selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, $-\text{F}$, $-\text{CF}_3$, $-\text{Cl}$, $-\text{Br}$, or $-\text{O}-\text{CH}_3$;

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wherein R^{4a} is selected from the group consisting of H, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, heteroaryl and aryl; and wherein NR^{4b} is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. A preferred R^{4a} group is the group hydrogen (H); and $(L_4)-$ is a divalent group selected from;



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where R₄₀, R₄₁, R₄₂, and R₄₃ are each independently selected from hydrogen or C₁-C₈ alkyl.

R₁₆ is selected from hydrogen, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio C₁-C₈ haloalkyl, C₁-C₈ hydroxyalkyl, and halo.

R₁₃ is selected from hydrogen and C₁-C₈ alkyl, C₁-C₈ alkoxy, -S-(C₁-C₈ alkyl), C₁-C₈ haloalkyl, C₁-C₈ phenyl, halophenyl, hydroxyalkyl, and halo, and t is an integer from 0 to 5.

Preferred specific compounds (and all pharmaceutically acceptable salts, solvates and prodrug derivatives thereof) which are illustrative of the compounds of the invention are as follow:

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine ;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester;

13-06-2001

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N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]glycine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-alanine;

5 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-alanine;

10 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-leucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-leucine;

15 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester;

20 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

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AMENDED SHEET

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N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

5 [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid dimethyl ester

10 [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester;

15 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine;

20 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine methyl ester; and

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine.

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The salts of the above indole compounds represented by formulae (I) and (II) are an additional aspect of the invention. In those instances where the compounds of the invention possess acidic or basic functional groups various salts may be formed which are more water soluble and physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion exchange resin.

Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention, for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous bases of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate,

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bitartrate, borate, bromide, camsylate, carbonate,
chloride, clavulanate, citrate, chloride, edetate,
edisylate, estolate, esylate, fluoride, fumarate,
gluceptate, gluconate, glutamate, glycolylarsanilate,
5 hexylresorcinate, bromide, chloride, hydroxynaphthoate,
iodide, isothionate, lactate, lactobionate, laurate,
malate, malseate, mandelate, mesylate, methylbromide,
methylnitrate, methylsulfate, mucate, napsylate, nitrate,
oleate, oxalate, palmitate, pantothenate, phosphate,
10 polygalacturonate, salicylate, stearate, subacetate,
succinate, tannate, tartrate, tosylate, trifluoroacetate,
trifluoromethane sulfonate, and valerate.

Certain compounds of the invention may possess one or
15 more chiral centers and may thus exist in optically active
forms. Likewise, when the compounds contain an alkenyl or
alkenylene group there exists the possibility of cis- and
trans- isomeric forms of the compounds. The R- and S-
isomers and mixtures thereof, including racemic mixtures
20 as well as mixtures of cis- and trans- isomers, are
contemplated by this invention. Additional asymmetric
carbon atoms can be present in a substituent group such as
an alkyl group. All such isomers as well as the mixtures
thereof are intended to be included in the invention. If
25 a particular stereoisomer is desired, it can be prepared
by methods well known in the art by using stereospecific

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reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods.

- 5 For example, a racemic mixture may be reacted with a single enantiomer of some other compound. This changes the racemic form into a mixture of diastereomers and diastereomers, because they have different melting points, different boiling points, and different solubilities can
10 be separated by conventional means, such as crystallization.

Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically cleavable
15 groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative
20 form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such
25 as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides

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prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters as prodrugs are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, morpholinoethyl, and N,N-diethylglycolamido.

10

N,N-diethylglycolamido ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) with 2-chloro-N,N-diethylacetamide (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA; Item No. 25,099-6).

15

Morpholinylethyl ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) 4-(2-chloroethyl)morpholine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C4,220-3).

20

a) The 1H-indole-3-glyoxylamide amino derivative compounds of the invention are prepared by room temperature base catalyzed condensation of the amino acid protected at the acid terminus by protecting group

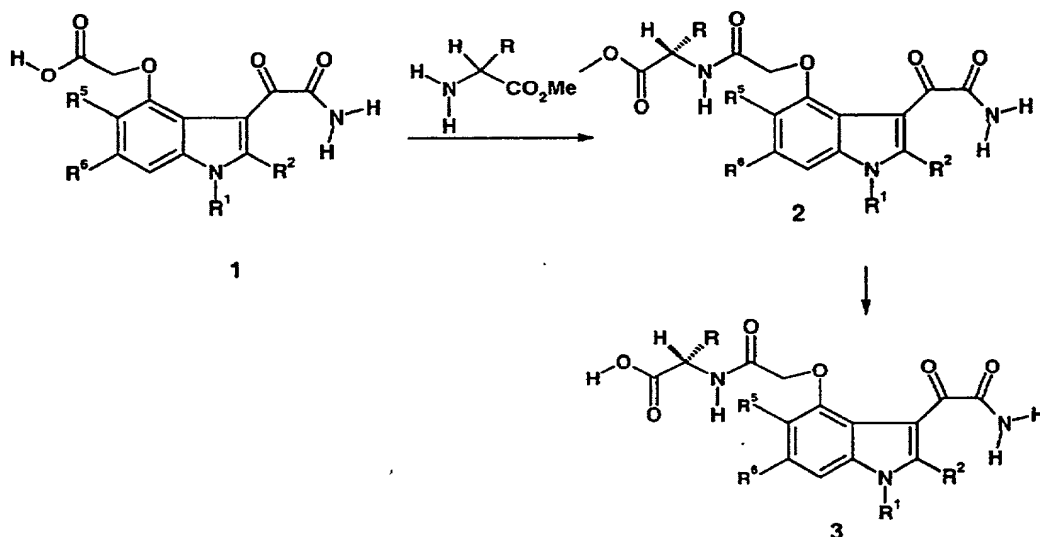
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known in the literature but preferably as the methyl ester with the 1H-indole-3-glyoxylamide acid derivative compound of formula (1) as shown in Scheme I:

5

Scheme 1



Typically, the condensation or coupling is performed in a solvent such a dimethyl formamide, tetrahydrofuran or aqueous mixtures of the like. In general protic solvents are preferred for the purpose of this invention. The reaction is catalyzed by a base including weak organic or inorganic bases. Organic bases such as collidine are preferred. The reaction is also preferably run in the presence of agents that retard or reduce racemization of the amino acid or its

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derivative, such as for example, benzotriazolyl-N-oxy-tris(dimethylamino)phosphonium hexafluorophosphate.

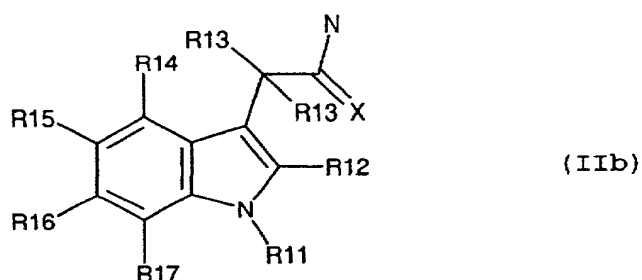
Upon completion of the reaction, the mixture is concentrated in vacuo. The resulting product mixture is chromatographed to obtain the target compound.

One of skill in the art is aware that the derivatives of the acid such as the acid salt or the methyl ester of the acid, can be reacted with the amino acid or derivatives thereof to obtain the protected compound 2 or a corresponding derivative. Such methods are well known in the arts and can be found in reference texts such as for example J. March Advanced Organic Chemistry, Wiley Interscience publishers, New York, N.Y., 1985, and R. C. Larock Comprehensive Organic Transformations, VCH Publishers, New York, N.Y., 1989. The protected compounds of formula (2) are also useful sPLA₂ inhibitors and are also compounds of this invention.

b) 1H-indole-3-acetamide amino acid derivative sPLA₂ inhibitors are similarly prepared by condensation of the protected amino acid with the 1H-indole-3-acetamide sPLA₂ inhibitor. The 1H-indole-3-acetamide sPLA₂ inhibitors and methods of making them are set out in U.S. Patent No. 5,684,034, the entire disclosure of which is incorporated herein by reference. Indole-3-acetamide

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amino acid derivative sPLA2 inhibitors of this invention are represented by compounds of formula (IIb), and pharmaceutically acceptable salts and prodrug derivatives thereof,



5

wherein ;

X is oxygen or sulfur;

R₁₁ is selected from groups (i), (ii) (iii) and (iv)

10 where;

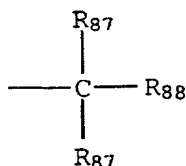
(i) is C₆-C₂₀ alkyl, C₆-C₂₀ alkenyl, C₆-C₂₀ alkynyl, C₆-C₂₀ haloalkyl, C₄-C₁₂ cycloalkyl, or

(ii) is aryl or aryl substituted by halo, nitro, -CN, -CHO, -OH, -SH, C₁-C₁₀ alkyl, C₁-C₁₀ alkylthio, C₁-
15 C₁₀ alkoxy, carboxyl, amino, or hydroxyamino; or

(iii) is -(CH₂)_n-(R₈₀), or -(NH)-(R₈₁), where n is 1 to 8, and R₈₀ is a group recited in (i), and R₈₁ is selected from a group recited in (i) or (ii);

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(iv) is



where R₈₇ is hydrogen or C₁-C₁₀ alkyl, and R₈₈ is selected from the group; phenyl, naphthyl, indenyl, and biphenyl, unsubstituted or substituted by halo, -CN, -CHO, -OH, -SH, C₁-C₁₀ alkylthio, C₁-C₁₀ alkoxy, phenyl, nitro, C₁-C₁₀ alkyl, C₁-C₁₀ haloalkyl, carboxyl, amino, hydroxyamino; or a substituted or unsubstituted 5 to 8 membered heterocyclic ring;

10 R₁₂ is halo, C₁-C₂ alkylthio, C₁-C₂ alkyl, C₁-C₂ alkyaryl or C₁-C₂ alkoxy;

each R₁₃ is independently hydrogen, halo, or methyl;

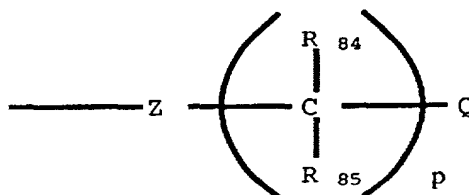
R₁₄ is the group -L_C-[acylamino acid], wherein the acylamino acid group is -C(O)-NR^{14a}R^{14b} wherein R^{14a} is selected from the group consisting of H, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, heteroaryl; and -L_C- is as defined *supra*, and wherein NR^{14b} is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. Most preferred are compounds of formula II wherein the group R^{14a} is a hydrogen atom (H). A preferred source of the amino acid residue NR^{14b} is an amino acid selected from the group comprising isoleucine, valine, phenylalanine,

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aspartic acid, leucine, glycine and isomers and derivatives thereof;

R₁₅ is selected from hydrogen, a non-interfering substituent, or the group, -(L_a)-(acidic group); wherein
 5 -(L_a)-, is an acid linker having an acid linker length of 1 to 8;

R₁₆ and R₁₇ are each independently hydrogen, C₁-C₁₀ alkyl, C₁-C₁₀ alkenyl, C₁-C₁₀ alkynyl, C₃-C₈ cycloalkyl, aryl, aralkyl, or any two adjacent hydrocarbyl groups in
 10 the set R₁₅, R₁₆, and R₁₇, combine with the ring carbon atoms to which they are attached to form a 5 or 6 membered substituted or unsubstituted carbocyclic ring; or C₁-C₁₀ haloalkyl, C₁-C₁₀ alkoxy, C₁-C₁₀ haloalkoxy, C₄-C₈ cycloalkoxy, phenoxy, halo, hydroxy, carboxyl, -SH, -CN,
 15 C₁-C₁₀ alkylthio, arylthio, thioacetal, -C(O)O(C₁-C₁₀ alkyl), hydrazide, hydrazino, hydrazido, -NH₂, -NO₂, -NR₈₂R₈₃, and -C(O)NR₈₂R₈₃, where, R₈₂ and R₈₃ are independently hydrogen, C₁-C₁₀ alkyl, C₁-C₁₀ hydroxyalkyl, or taken together with N, R₈₂ and R₈₃ form a 5- to 8-
 20 membered heterocyclic ring; or a group having the formula;



where,

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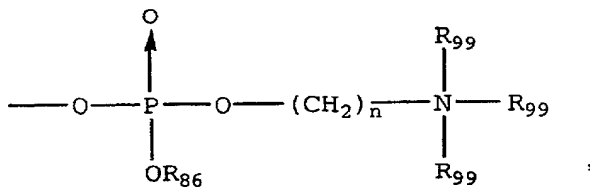
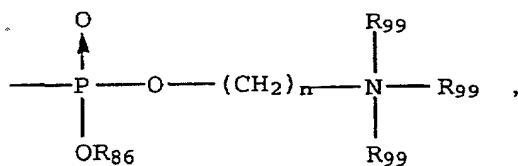
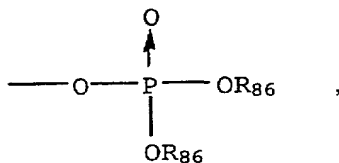
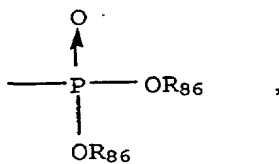
R₈₄ and R₈₅ are each independently selected from hydrogen, C₁-C₁₀ alkyl, hydroxy, or R₈₄ and R₈₅ taken together are =O;

p is 1 to 5,

5 Z is a bond, -O-, -N(C₁-C₁₀ alkyl)-, -NH-, or -S-;

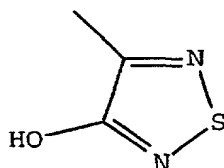
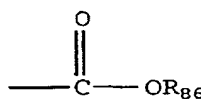
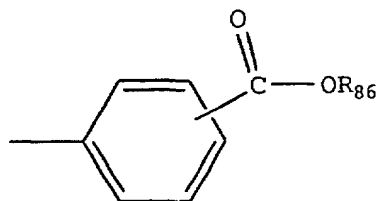
and

Q is -CON(R₈₂R₈₃), -5-tetrazolyl, -SO₃H,



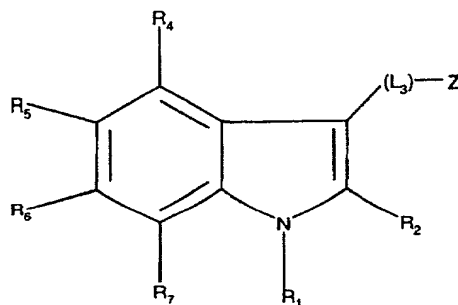
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where n is 1 to 8, R₈₆ is independently selected from
hydrogen, a metal, or C₁-C₁₀ alkyl, and R₉₉ is selected
5 from hydrogen or C₁-C₁₀ alkyl.

c) Indole-3-Oxime amide compounds of the invention
are represented by compounds of formula (III) or a
pharmaceutically acceptable salt, solvate or prodrug
10 thereof;



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wherein ;

R_1 is selected from groups (a), (b), and (c)

wherein;

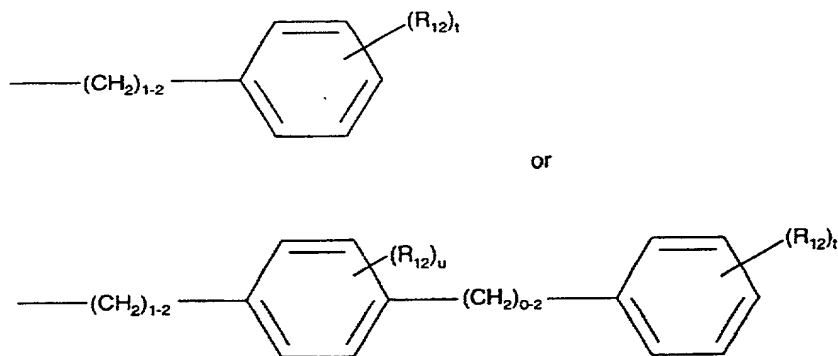
5 (a) is C7-C20 alkyl, C7-C20 haloalkyl, C7-C20 alkenyl, C7-C20 alkynyl, carbocyclic radical, or heterocyclic radical, or

(b) is a member of (a) substituted with one or more independently selected non-interfering

10 substituents; or

(c) is the group $-(L_1)-R_{11}$; where, $-(L_1)-$ is a divalent linking group of 1 to 8 atoms and where R_{11} is a group selected from (a) or (b).

15 Particularly preferred are compounds wherein for R_1 the combined group $-(L_1)-R_{11}$ is selected from the group consisting of



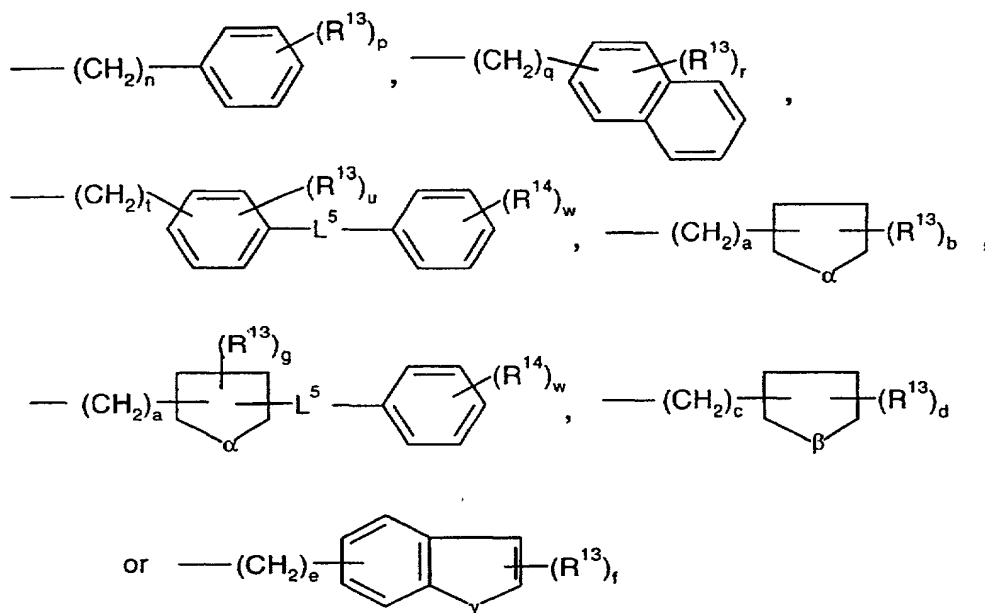
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where R_{12} is a radical independently selected from halo, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, $-S-(C_1-C_8 \text{ alkyl})$, $-O-(C_1-C_8 \text{ alkyl})$ and C_1 - C_8 haloalkyl where t is a number from 0 to 5 and u is a number from 0 to 4.

5

Also preferred for R_{11} is $-(CH_2)_m-R^{12}$ wherein m is an integer from 1 to 6, and R^{12} is (d) a group represented by the formula:



10

wherein a , c , e , n , q , and t are independently an integer from 0 to 2, R^{13} and R^{14} are independently selected from a halogen, C_1 to C_8 alkyl, C_1 to C_8 alkyloxy, C_1 to C_8 alkylthio, aryl, heteroaryl, and C_1 to

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C₈ haloalkyl, α is an oxygen atom or a sulfur atom, L⁵

is a bond, -(CH₂)^v-,

-C=C-, -CC-, -O-, or -S-, v is an integer from 0 to 2, β

is -CH₂- or -(CH₂)₂-, γ is an oxygen atom or a sulfur

5 atom, b is an integer from 0 to 3, d is an integer from

0 to 4, f, p, and w are independently an integer from 0

to 5, r is an integer from 0 to 7, and u is an integer

from 0 to 4, or is (e) a member of (d) substituted with

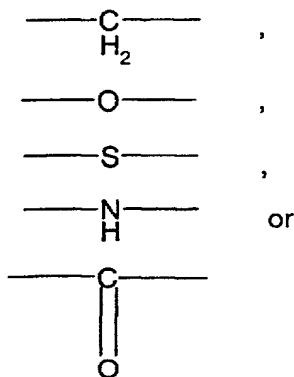
at least one substituent selected from the group

10 consisting of C₁ to C₆ alkyl, C₁ to C₈ alkyloxy, C₁ to C₈

haloalkyloxy, C₁ to C₈ haloalkyl,* aryl, and a halogen.

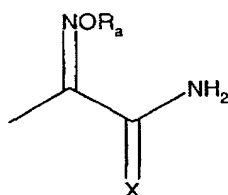
R₂ is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

15 -(L₃)- Z, is the group where -(L₃)- is a divalent linker group selected from a bond or a divalent group selected from:



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and Z is selected from an oxime amide or oxime thioamide group represented by the formulae,



5

wherein, X is oxygen or sulfur; and R_a is selected from hydrogen, C₁-C₈ alkyl, aryl, C₁-C₈ alkaryl, C₁-C₈ alkoxy, aralkyl and -CN;

10 R_4 is the group, $-(\text{L}_C)-(\text{acylamino acid group})$; wherein $-(\text{L}_C)-$, is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

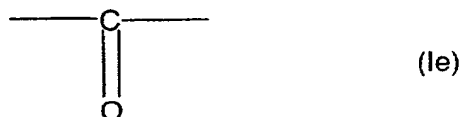
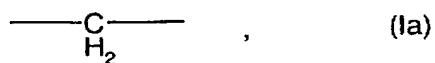
R_5 is selected from hydrogen, a non-interfering substituent, or the group, $-(\text{L}_A)-(\text{acidic group})$; wherein
15 $-(\text{L}_A)-$, is an acid linker having an acid linker length of 1 to 8.

R_6 and R_7 are selected from hydrogen, non-interfering substituent, carbocyclic radical,
20 carbocyclic radical substituted with non-interfering substituent(s), heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

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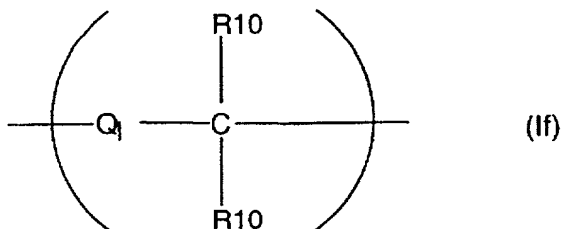
Preferred Subgroups of Compounds of Formula (III):
Preferred R₁ substituents:

- A preferred subclass of compounds of formula (III)
 5 are those where for R₁ the divalent linking group -(L₁)-
 is a group represented by any one of the following
 formulae (Ia), (Ib), (Ic), (Id), (Ie), or (If):



10

or



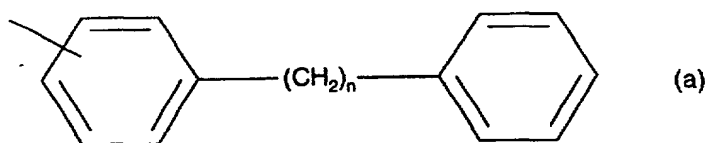
- 15 where Q₁ is a bond or any of the divalent groups (Ia),
 (Ib), (Ic), (Id), (Ie), and (If) and each R₁₀ is

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independently hydrogen, C₁₋₈ alkyl, C₁₋₈ haloalkyl or C₁₋₈ alkoxy.

Particularly preferred as the linking group -(L₁)- of
5 R₁ is an alkylene chain of 1 or 2 carbon atoms, namely,
-(CH₂)- or -(CH₂-CH₂)-.

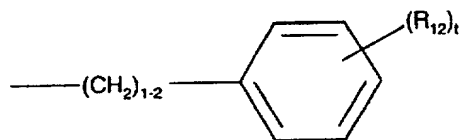
The preferred group for R₁₁ is a substituted or
unsubstituted group selected from the group consisting of
10 C₅-C₁₄ cycloalkyl, C₅-C₁₄ cycloalkenyl, phenyl, naphthyl,
norbornanyl, bicycloheptadienyl, tolulyl, xylenyl,
indenyl, stilbenyl, terphenyl, diphenylethylenyl,
phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl,
biphenyl, bibenzylyl and related bibenzylyl homologues
15 represented by the formula (a);



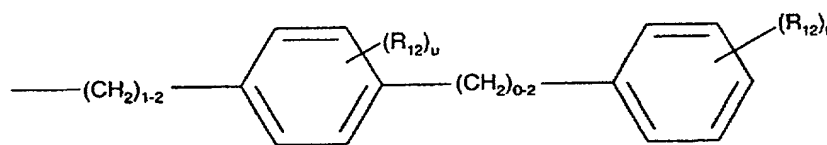
where n is a number from 1 to 8.

20 Particularly preferred are compounds wherein for R₁
the combined group -(L₁)-R₁₁ is selected from the group
consisting of

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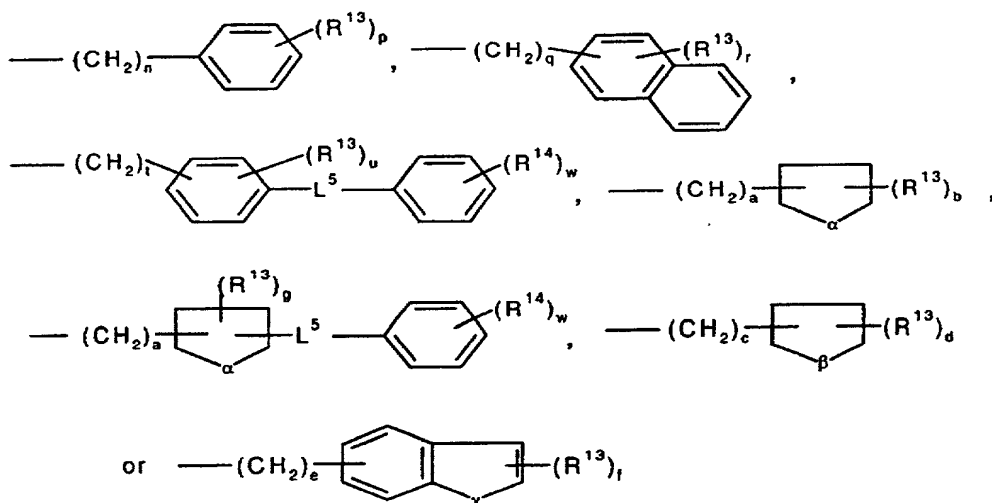


or



where R_{12} is a radical independently selected from halo, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, $-S-(C_1-C_8 \text{ alkyl})$, $-O-(C_1-C_8$
 5 alkyl) and C_1 - C_8 haloalkyl where t is a number from 0 to 5 and u is a number from 0 to 4.

Also preferred for R_{11} is $-(CH_2)_m-R^{12}$ wherein m is an integer from 1 to 6, and R^{12} is (d) a group represented by
 10 the formula:



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wherein a, c, e, n, q, and t are independently an integer from 0 to 2, R¹³ and R¹⁴ are independently selected from a halogen, C₁ to C₈ alkyl, C₁ to C₈ alkyloxy, C₁ to C₈ alkylthio, aryl, heteroaryl, and C₁ to C₈ haloalkyl, α is an oxygen atom or a sulfur atom, L⁵ is a bond, -(CH₂)^v-, -C=C-, -CC-, -O-, or -S-, v is an integer from 0 to 2, β is -CH₂- or -(CH₂)₂-, γ is an oxygen atom or a sulfur atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group consisting of C₁ to C₆ alkyl, C₁ to C₈ alkyloxy, C₁ to C₈ haloalkyloxy, C₁ to C₈ haloalkyl, aryl, and a halogen.

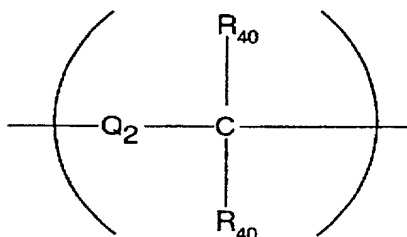
Preferred R₂ substituents:

R₂ is preferably selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, -O-(C₁-C₃ alkyl), -S-(C₁-C₃ alkyl), -C₃-C₄ cycloalkyl -CF₃, halo, -NO₂, -CN, -SO₃. Particularly preferred R₂ groups are selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, -CF₃, -Cl, -Br, or -O-CH₃.

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Preferred R₄ substituents:

Another preferred subclass of compounds of formula (III) are those wherein R₄ is a substituent having an acylamino acid linker with an acylamino acid linker length of 2 or 3 and the acylamino acid linker group, -(L_C)-, for R₄ is selected from a group represented by the formula;



10

where Q₂ is selected from the group -(CH₂)-, -O-, -NH-, -C(O)-, and -S-, and each R₄₀ is independently selected from hydrogen, C₁-C₈ alkyl, aryl, C₁-C₈ alkaryl, C₁-C₈ alkoxy, aralkyl, and halo. Most preferred are compounds where the acylamino acid linker, -(L_C)-, for R₄ is selected from the specific groups;

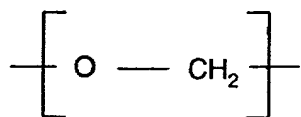
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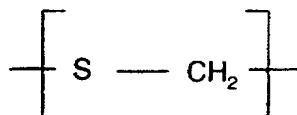
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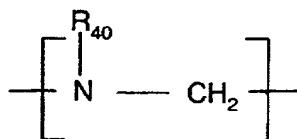
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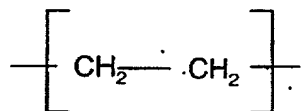
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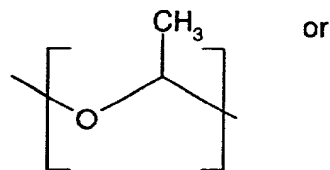
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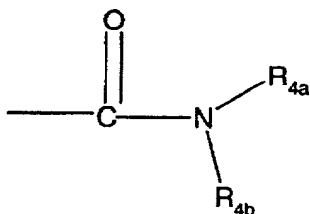


,

where R₄₀ is hydrogen or C₁ -C₈ alkyl.

Preferred as the (acylamino acid group) in the group R₄

5 is the group:



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wherein R^{4a} is selected from the group consisting of H,
(C₁-C₆)alkyl, (C₁-C₆)alkoxy, heteroaryl and aryl; and
wherein NR^{4b} is an amino acid residue of either a natural
or unnatural amino acid with the nitrogen atom being part
5 of the amino group of the amino acid. A preferred R^{4a}
group is the group hydrogen (H). A preferred source of
amino acid residue is the amino acid group selected from
the group comprising isoleucine, valine, phenylalanine,
aspartic acid, leucine, glycine and isomers and
10 derivatives thereof.

A salt or a prodrug derivative of the (acylamino
acid group) is also a suitable substituent.

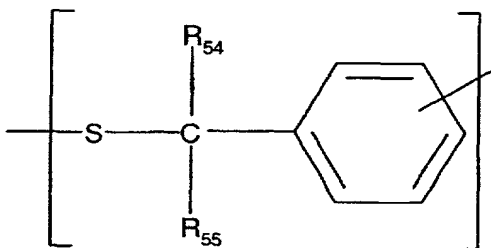
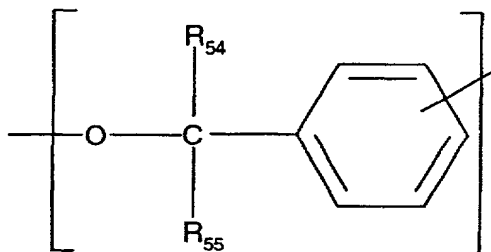
15 Particularly preferred are R^{4b} groups that combine
with the nitrogen atom to represent amino acid groups
selected from: glycine, glycine methyl ester, L-
alanine, L-alanine methylester, L-leucine, L-leucine
methyl ester, L-aspartic acid, L-aspartic acid dimethyl
20 ester, L-phenyl alanine, L-phenylalanine methyl ester,
malonic acid, malonic acid dimethylester, L- valine, L-
valine methyl ester, L-isoleucine, L-isoleucine methyl
ester, or salt, and derivatives thereof.

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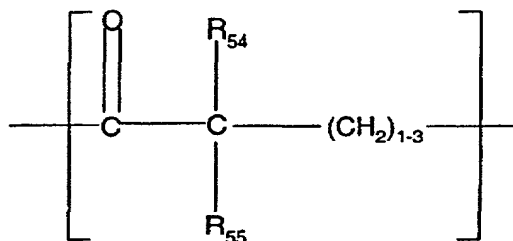
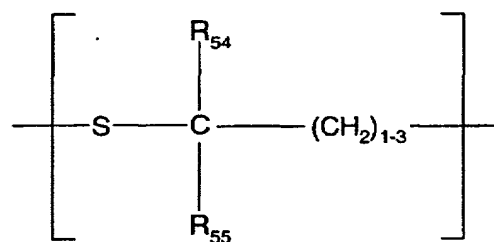
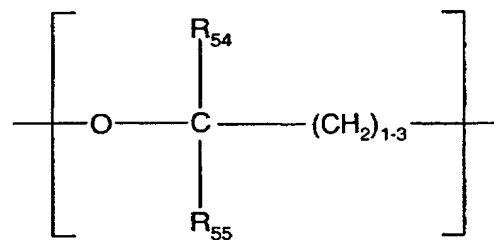
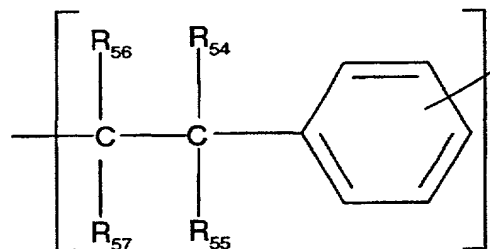
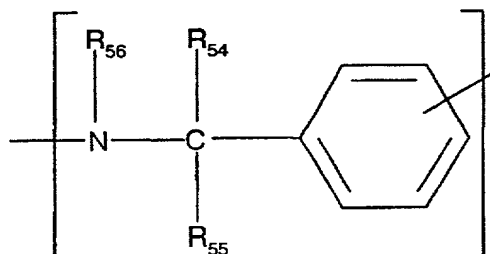
Preferred R₅ Substituents:

Preferred acid linker, $-(L_a)-$, for R₅ is selected from the group consisting of;

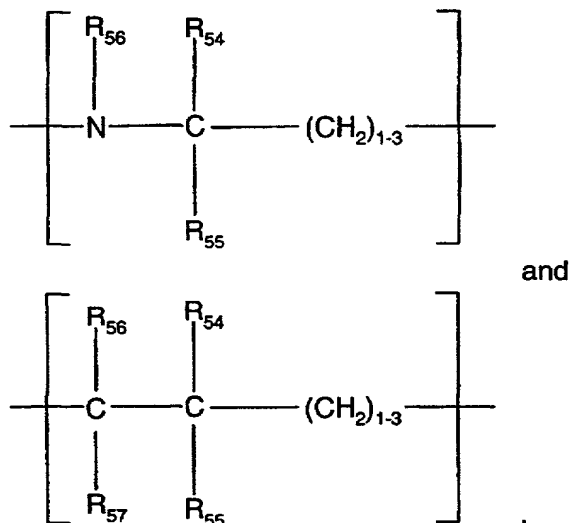
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-59-



wherein R₅₄, R₅₅, R₅₆ and R₅₇ are each independently hydrogen, C₁-C₈ alkyl, C₁-C₈ haloalkyl, aryl, C₁-C₈ alkoxy, or halo. Preferred (acidic group) for R₅ is selected from the group consisting of -CO₂H, -SO₃H and -P(O)(OH)₂

Preferred R₆ and R₇ substituents:

Another preferred subclass of compounds of formula (III) are those wherein for R₆ and R₇ the non-interfering substituent is independently methyl, ethyl, propyl, isopropyl, thiomethyl, -O-methyl, C₄-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C₁-C₆ alkoxy, C₂-C₆ alkenyloxy, C₂-C₆ alkynyloxy, C₂-C₁₂ alkoxyalkyl, C₂-C₁₂

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- alkoxyalkyloxy, C₂-C₁₂ alkylcarbonyl, C₂-C₁₂
alkylcarbonylamino, C₂-C₁₂ alkoxyamino, C₂-C₁₂
alkoxyaminocarbonyl, C₁-C₁₂ alkylamino, C₁-C₆ alkylthio,
C₂-C₁₂ alkylthiocarbonyl, C₁-C₆ alkylsulfinyl, C₁-C₆
5 alkylsulfonyl, C₂-C₆ haloalkoxy, C₁-C₆
haloalkylsulfonyl, C₂-C₆ haloalkyl, C₁-C₆ hydroxyalkyl,
-C(O)O(C₁-C₆ alkyl), -(CH₂)_n-O-(C₁-C₆ alkyl), benzyloxy,
phenoxy, phenylthio, -(CONHSO₂R), -CHO, amino, amidino,
bromo, carbamyl, carboxyl, carbalkoxy, -(CH₂)_n-CO₂H,
10 chloro, cyano, cyanoguanidinyll, fluoro, guanidino,
hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino,
iodo, nitro, phosphono, -SO₃H, thioacetal, thiocarbonyl,
and carbonyl; where n is from 1 to 8.

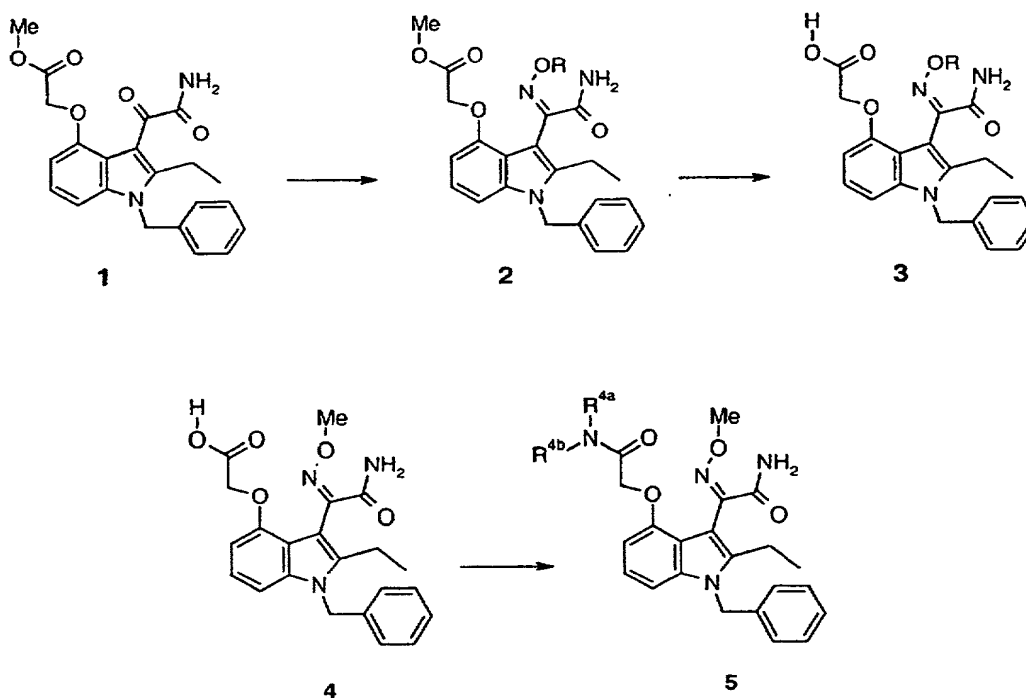
- 15 Most preferred as non-interfering substituents are
methyl, ethyl, propyl, and isopropyl.

The indole-3-oxime compounds of the invention can be
prepared following protocol of scheme 2 below;

20

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Scheme 2



5

To introduce the oxime functionality, the methyl ester of the glyoxylamide (compound 10 in scheme 1, compound 1 in scheme 2, *supra.*) is heated with hydroxylamine hydrochloride (when R is H) in a THF/methanol mixture for 8 hours or until the reaction was deemed complete. The reaction product is isolated by chromatography or other known laboratory procedure to afford a white solid. Substituted oximes such as when R is methyl, ethyl, phenyl or other substituent can be prepared by reacting the corresponding substituted hydroxylamine hydrochloride or free base with the

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glyoxylamide as described *supra*. The ester functionality at the 4 or 5 position on the indole nucleus, as in for example, compound 2, can be: (a) converted to the acid by hydrolysis using lithium hydroxide or other known ester hydrolysis methods to afford compounds of formula 3, or (b) converted to an amide functionality directly or via the acid functionality to afford compounds of formula 4. General procedures for the conversion of organic acids to amino acid are well known to artisans in the field, and have been documented in general reference texts including, for example, J. March Advanced Organic Chemistry, Wiley Interscience publishers, New York, N.Y, 1985, and R. C. Larock Comprehensive Organic Transformations, VCH Publishers, New York, N.Y, 1989.

15

The oxime acid compounds of formula 3 such as the methyloxime compound such as that of formula 4 can be converted to the corresponding amino acid derivative via the methylester by coupling with various amino acids by general coupling procedures known to one skilled in the art. Additional references, or procedures are found in J. March Advanced Organic Chemistry, Wiley Interscience publishers, New York, N.Y, 1985; R. C. Larock Comprehensive Organic Transformations, VCH Publishers, New York, N.Y, 1989 and J. Jones Amino Acids and Peptide

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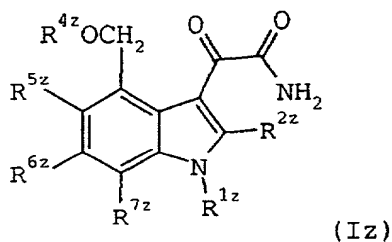
Synthesis, Oxford Science Publications, Stephen G. Davis,
Editor, Oxford University Press Inc., New York, NY, 1992.

5 **III. Method of Making the 1H-Indole-3-Glyoxylamide
Starting Material for Preparing the Compounds of the
Invention:**

 The synthesis of the indole compounds of the
10 invention (viz., Compounds of Formulae I and II) can be
accomplished by well known methods as recorded in the
chemical literature. In particular, the indole starting
materials may be prepared by the synthesis schemes
taught in US Patent No. 5,654,326; the disclosure of
15 which is incorporated herein by reference. Another
method of making 1H-indole-3-glyoxylamide sPLA₂
inhibitors is described in United States Patent
Application Serial No. 09/105381, filed June 26, 1998
and titled, "Process for Preparing 4-substituted 1-H-
20 Indole-3-glyoxyamides" the entire disclosure of which is
incorporated herein by reference.

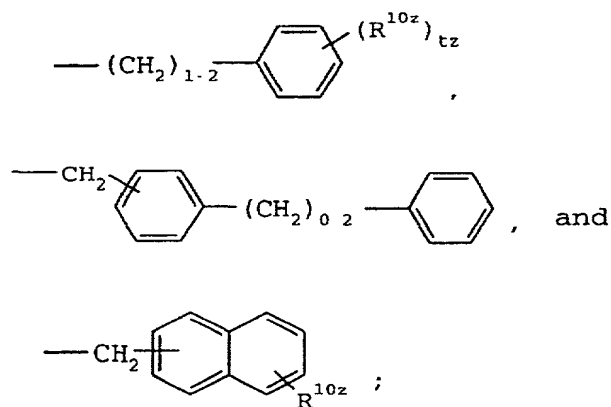
 United States Patent Application Serial
No. 09/105381 discloses the following process having
25 steps (a) thru (i):
Preparing a compound of the formula (Iz) or a
pharmaceutically acceptable salt or prodrug derivative
thereof

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5 wherein:

R^{1z} is selected from the group consisting of -C₇-C₂₀ alkyl,



where

10 R^{10z} is selected from the group consisting of halo, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, -S-(C₁-C₁₀ alkyl) and halo(C₁-C₁₀)alkyl, and tz is an integer from 0 to 5 both inclusive;

R^{2z} is selected from the group consisting of
15 hydrogen, halo, C₁-C₃ alkyl, C₃-C₄ cycloalkyl, C₃-C₄

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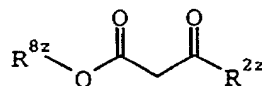
cycloalkenyl, -O-(C₁-C₂ alkyl), -S-(C₁-C₂ alkyl), aryl, aryloxy and HET;

R^{4z} is the group -CO₂H, or salt and prodrug derivative thereof; and

- 5 R^{5z}, R^{6z} and R^{7z} are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy, halo(C₂-C₆)alkyl, bromo, chloro, fluoro, iodo and aryl;

which process comprises the steps of:

- 10 a) halogenating a compound of formula Xz

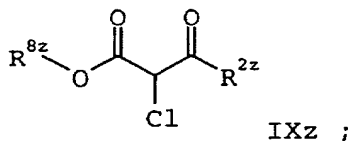


Xz

where R^{8z} is (C₁-C₆)alkyl, aryl or HET;

with SO₂Cl₂ to form a compound of formula

15 IX

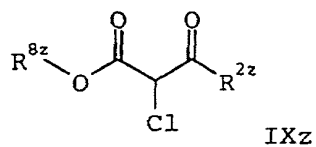


IXz ;

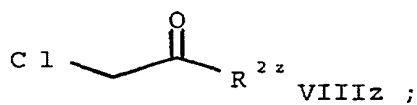
- b) hydrolyzing and decarboxylating a compound of formula IXz

20

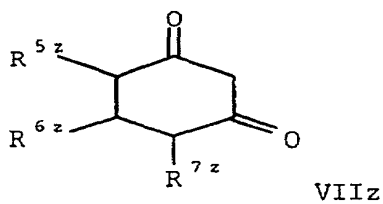
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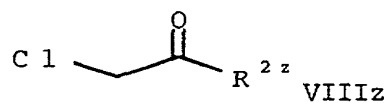
to form a compound of formula VIIIz



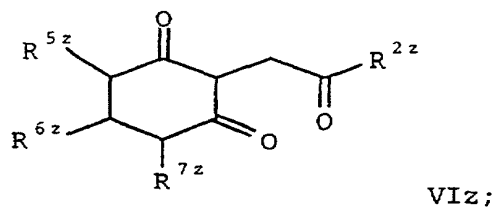
c) alkylating a compound of formula VIIz



with a compound of formula VIIIz

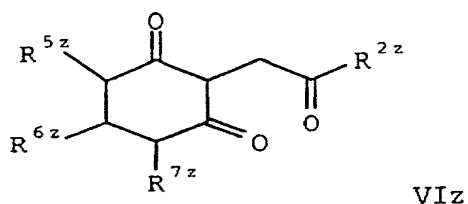


to form a compound of formula VIz



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- d) aminating and dehydrating a compound of formula VIz

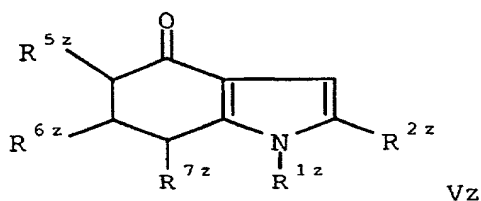


5

with an amine of the formula $R^{1z}NH_2$ in the presence of a solvent that forms an azeotrope with water to form a compound of formula Vz;

10

- e) oxidizing a compound of formula Vz



15

by refluxing in a polar hydrocarbon solvent having a boiling point of at least 150 °C and a dielectric constant of at least 10 in the presence of a catalyst to form a compound of formula IVz

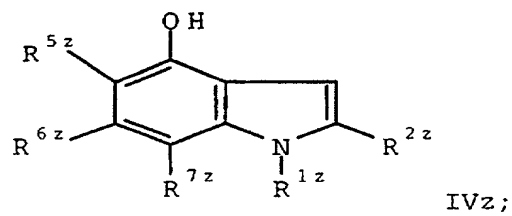
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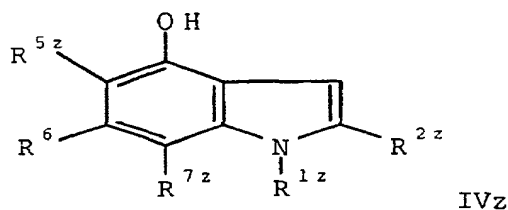
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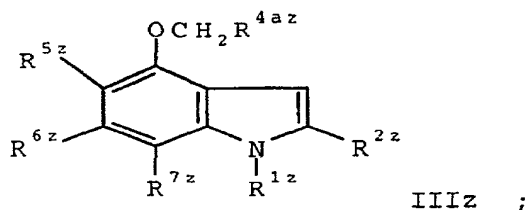


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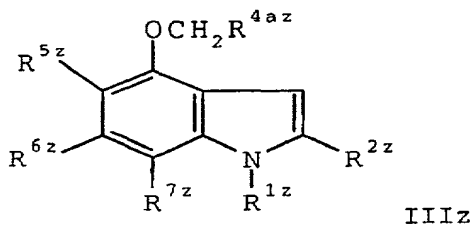
f) alkylating a compound of the formula IVz



with an alkylating agent of the formula XCH_2R^{4az} where X is a leaving group and R^{4az} is $-CO_2R^{4b}$, where R^{4b} is an acid protecting group to form a compound of formula IIIz

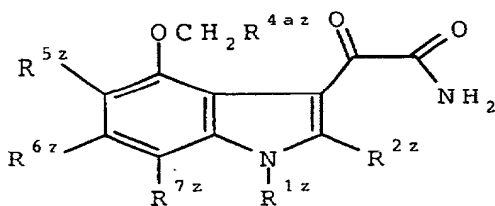


g) reacting a compound of formula IIIz



with oxalyl chloride and ammonia to form a compound of formula IIz

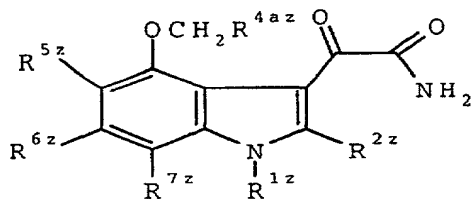
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IIz; and

5

- h) optionally hydrolyzing a compound of formula IIz



10

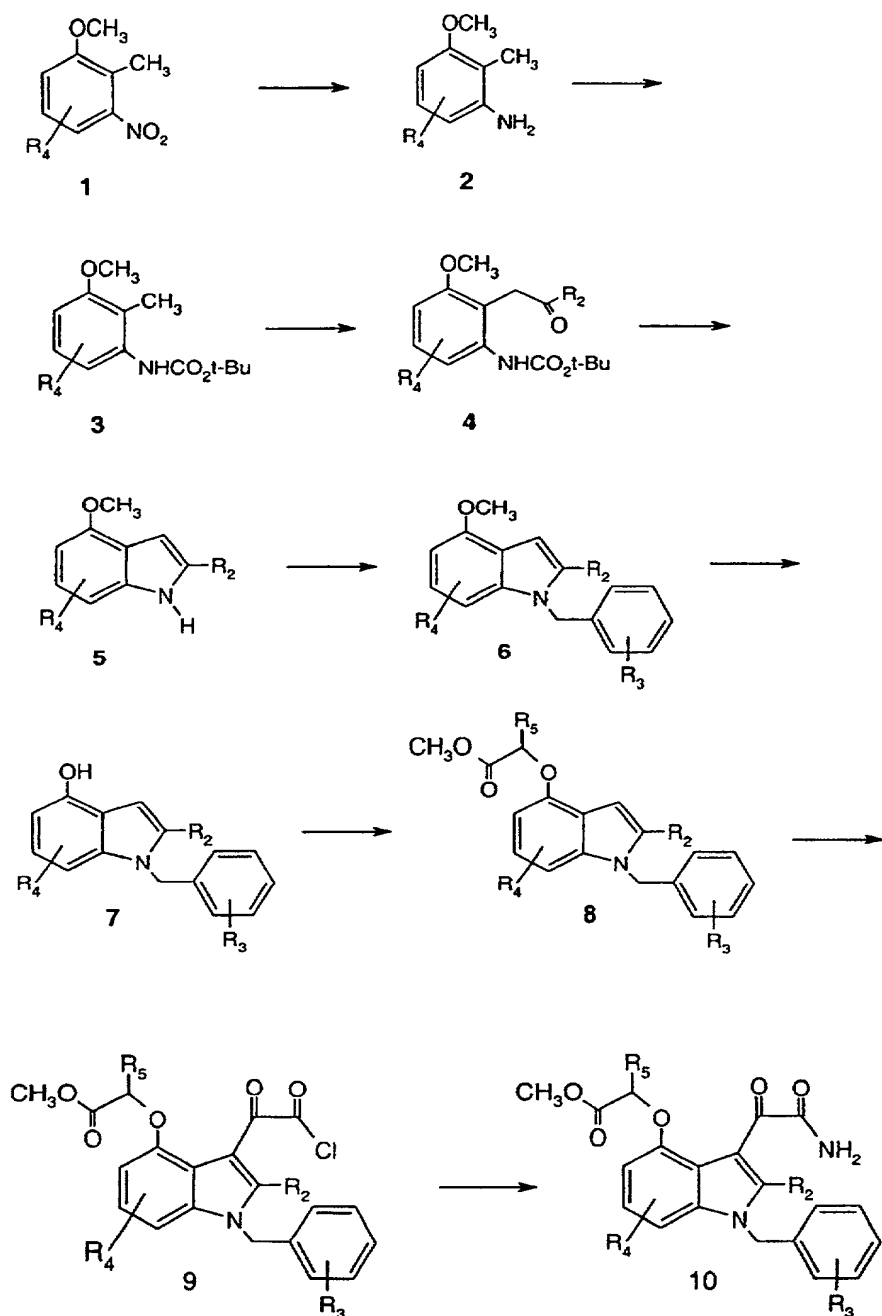
IIz

to form a compound of formula Iz.

An alternative protocol useful for the synthesis of the starting material is shown in Scheme 1 below:

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Scheme 1



5 The synthesis of indole-3-oxime amides (compound of formula I and II, supra.) of this invention uses

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as starting material the glyoxamide ((3-(2-amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl)oxy)acetic acid methyl ester, compound 10, *supra*. This starting material is prepared as set out in the preceding section or by the method of Example 9 of U.S. Patent No. 5,654,326 (the disclosure of which is incorporated herein by reference).

To obtain the glyoxylamide starting material substituted in the 4-position with an (acidic group) linked through an oxygen atom, the reactions outlined in the scheme *supra*, are used (for conversions 1 through 5, see ref. Robin D. Clark, Joseph M. Muchowski, Lawrence E. Fisher, Lee A. Flippin, David B. Repke, Michel Souchet, *Synthesis*, 1991, 871-878, the disclosures of which are incorporated herein by reference). The starting material ortho-nitrotoluene, 1, is readily reduced to 2-methyl,3-methoxyaniline, 2. Reduction of 1 is by the catalytic hydrogenation of the corresponding nitrotoluene using palladium on carbon as catalyst. The reduction can be carried out in ethanol or tetrahydrofuran (THF) or a combination of both, using a low pressure of hydrogen. The aniline 2, obtained, is converted to the N-tert-butyloxycarbonyl derivative 3, in good yield, on heating with di-tert-butyl dicarbonate in THF at reflux temperature. The dilithium salt of the dianion of 3 is

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generated at -40 to -20°C in THF using sec-butyllithium and reacted with the appropriately substituted N-methoxy-N-methylalkanamide to form the ketone 4. This product (4) may be purified by crystallization from hexane, or reacted
5 directly with trifluoroacetic acid in methylene chloride to give the 1,3-unsubstituted indole 5. The 1,3-unsubstituted indole 5 is reacted with sodium hydride in dimethylformamide at room temperature (20-25°C) for 0.5-1.0 hour. The resulting sodium salt of 5 is treated with
10 an equivalent of arylmethyl halide and the mixture stirred at a temperature range of 0-100°C, usually at ambient room temperature, for a period of 4 to 36 hours to give the 1-arylmethylindole, 6. This indole, 6, is O-demethylated by stirring with boron tribromide in methylene chloride for
15 approximately 5 hours (see ref. Tsung-Ying Shem and Charles A Winter, *Adv. Drug Res.*, 1977, 12, 176, the disclosure of which is incorporated herein by reference). The 4-hydroxyindole, 7, is alkylated with an alpha bromoalkanoic acid ester in dimethylformamide (DMF) using
20 sodiumhydride as a base, with reaction condition of 5 to 6. The α -[(indol-4-yl)oxy]alkanoic acid ester, 8, is reacted with oxalyl chloride in methylene chloride to give 9, which is not purified but reacted directly with ammonia to give the glyoxamide 10.

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Glyoxamide starting material compounds substituted at the 5 position of the indole nucleus with an (acidic group) may be prepared by methods and starting materials shown in schemes 2 and 3 of Patent No. 5,654,326; the disclosure of which is incorporated herein by reference.

IV. Methods of Using the Compounds of the Invention:

The indole compounds described herein are believed to achieve their beneficial therapeutic action principally by direct inhibition of mammalian (including human) sPLA₂, and not by acting as antagonists for arachidonic acid, nor other active agents below arachidonic acid in the arachidonic acid cascade, such as 5-lipoxygenases, cyclooxygenases, and etc.

The method of the invention for inhibiting sPLA₂ mediated release of fatty acids comprises contacting mammalian sPLA₂ with an therapeutically effective amount of indole compounds corresponding to Formulae (I) or (II) as described herein including salt or a prodrug derivative thereof.

Another aspect of this invention is a method for treating Inflammatory Diseases such as inflammatory bowel disease, septic shock, adult respiratory distress

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syndrome, pancreatitis, trauma, bronchial asthma,
allergic rhinitis, rheumatoid arthritis, osteoarthritis,
and related diseases which comprises administering to a
mammal (including a human) a therapeutically effective
5 dose of the indole compound of the invention (see,
formulae I and II).

As previously noted the compounds of this invention
are useful for inhibiting sPLA₂ mediated release of
10 fatty acids such as arachidonic acid. By the term,
"inhibiting" is meant the prevention or therapeutically
significant reduction in release of sPLA₂ initiated
fatty acids by the compounds of the invention. By
"pharmaceutically acceptable" it is meant the carrier,
15 diluent or excipient must be compatible with the other
ingredients of the formulation and not deleterious to
the recipient thereof.

The specific dose of a compound administered
20 according to this invention to obtain therapeutic or
prophylactic effects will, of course, be determined by the
particular circumstances surrounding the case, including,
for example, the compound administered, the route of
administration and the condition being treated. Typical
25 daily doses will contain a non-toxic dosage level of from

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about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound of this invention.

Preferably compounds of the invention (per Formula I
5 or II) or pharmaceutical formulations containing these compounds are in unit dosage form for administration to a mammal. The unit dosage form can be a capsule or tablet itself, or the appropriate number of any of these. The quantity of Active ingredient in a unit dose of
10 composition may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the patient. The
15 dosage will also depend on the route of administration.

The compound can be administered by a variety of routes including oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, and
20 intranasal.

Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) a therapeutically effective amount of the indole compound of the invention
25 together with a pharmaceutically acceptable carrier or diluent therefor. The present pharmaceutical

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formulations are prepared by known procedures using well known and readily available ingredients.

In making the compositions of the present invention, the Active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the active compound.

The compounds of the present invention are preferably formulated prior to administration.

For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. For example, for intravenous injection the compounds of the invention may be dissolved in at a concentration of 2 mg/ml in a 4% dextrose/0.5% Na citrate aqueous solution. Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substances which may also

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act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

5 Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or
10 acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc.

In powders the carrier is a finely divided solid which is in admixture with the finely divided Active
15 ingredient. In tablets the Active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 1 to about 99 weight percent of the Active
20 ingredient which is the novel compound of this invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa
25 butter.

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Sterile liquid form formulations include suspensions, emulsions, syrups and elixirs.

The Active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both. The Active ingredient can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol. Other compositions can be made by dispersing the finely divided Active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The following pharmaceutical formulations 1 thru 8 are illustrative only and are not intended to limit the scope of the invention in any way. "Active ingredient", refers to a compound according to Formula (I) or (II) or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

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Formulation 2

A tablet is prepared using the ingredients below:

	<u>Quantity</u> <u>(mg/tablet)</u>
Active ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	<u>5</u>
Total	665 mg

5

The components are blended and compressed to form tablets each weighing 665 mg

Formulation 3

10 An aerosol solution is prepared containing the following components:

	<u>Weight</u>
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	<u>74.00</u>
Total	100.00

15 The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and

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diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

- 5 Tablets, each containing 60 mg of Active ingredient, are made as follows:

Active ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	<u>1 mg</u>
Total	150 mg

- The Active ingredient, starch and cellulose are
- 10 passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and
- 15 passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each
- 20 weighing 150 mg.

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Formulation 5

Capsules, each containing 80 mg of Active ingredient,
are made as follows:

5

Active ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	<u>2 mg</u>
Total	200 mg

The Active ingredient, cellulose, starch, and
magnesium stearate are blended, passed through a No. 45
mesh U.S. sieve, and filled into hard gelatin capsules in
200 mg quantities.

10

Formulation 6

Suppositories, each containing 225 mg of Active
ingredient, are made as follows:

Active ingredient	225 mg
Saturated fatty acid glycerides	<u>2,000 mg</u>
Total	2,225 mg

15

The Active ingredient is passed through a No. 60 mesh
U.S. sieve and suspended in the saturated fatty acid
glycerides previously melted using the minimum heat
necessary. The mixture is then poured into a suppository
mold of nominal 2 g capacity and allowed to cool.

20

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Formulation 7

Suspensions, each containing 50 mg of Active ingredient per 5 ml dose, are made as follows:

5

Active ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The Active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

10

Formulation 8

15

An intravenous formulation may be prepared as follows:

Active ingredient	100 mg
Isotonic saline	1,000 ml

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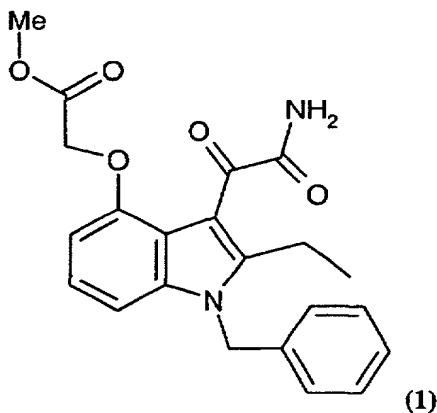
The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

5 All of the products of the Examples described below as well as intermediates used in the following procedures showed satisfactory nmr and IR spectra. They also had the correct mass spectral values.

10

Example 1

Preparation of [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester, a compound represented by the compound of formula (1) formula:



15

Part A. Preparation of 2-Ethyl-4-methoxy-1H-indole.

A solution of 140 mL (0.18 mol) of 1.3M sec-butyl lithium in cyclohexane was added slowly to N-tert-
20 butoxycarbonyl-3-methoxy-2-methylaniline (21.3g, 0.09 mol)

-85-

in 250 mL of THF keeping the temperature below -40°C with a dry ice-ethanol bath. The bath was removed and the temperature allowed to rise to 0°C and then the bath replaced. After the temperature had cooled to -60°C, 18.5g (0.18 mol) of N-methoxy-N-methylpropanamide in an equal volume of THF was added dropwise. The reaction mixture was stirred 5 minutes, the cooling bath removed and stirred an additional 18 hours. It was then poured into a mixture of 300 mL of ether and 400 mL of 0.5N HCl. The organic layer was separated, washed with water, brine, dried over MgSO_4 , and concentrated at reduced pressure to give 25.5g of a crude of 1-[2-(tert-butoxycarbonylamino)-6-methoxyphenyl]-2-butanone. This material was dissolved in 250 mL of methylene chloride and 50 mL of trifluoroacetic acid and stirred for a total of 17 hours. The mixture was concentrated at reduced pressure and ethyl acetate and water added to the remaining oil. The ethyl acetate was separated, washed with brine, dried (MgSO_4) and concentrated. The residue was chromatographed three times on silica eluting with 20% EtOAc/hexane to give 13.9g of 2-ethyl-4-methoxy-1H-indole.

Analyses for $\text{C}_{11}\text{H}_{13}\text{NO}$:

Calculated: C, 75.40; H, 7.48; N, 7.99

Found: C, 74.41; H, 7.64; N, 7.97.

25

Part B. Preparation of 2-Ethyl-4-methoxy-1-(phenylmethyl)-1H-indole.

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2-Ethyl-4-methoxy-1H-indole (4.2g, 24 mmol) was dissolved in 30 mL of DMF and 960mg (24 mmol) of 60% NaH/mineral oil was added. After 1.5 hours, 2.9 mL (24 mmol) of benzyl bromide was added. After 4 hours, the mixture was diluted with water and extracted twice with ethyl acetate. The combined ethyl acetate was washed with brine, dried (MgSO₄) and concentrated at reduced pressure. The residue was chromatographed on silica gel and eluted with 20% EtOAc/hexane to give 3.1g (49% yield) of 2-ethyl-4-methoxy-1-(phenylmethyl)-1H-indole.

Part C. Preparation of 2-Ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole.

3.1g (11.7 mmol) of 2-ethyl-4-methoxy-1-(phenylmethyl)-1H-indole was O-demethylated by treating it with 48.6 mL of 1M BBr₃ in methylene chloride with stirring at room temperature for 5 hours, followed by concentration at reduced pressure. The residue was dissolved in ethyl acetate, washed with brine and dried (MgSO₄). After concentrating at reduced pressure, the residue was chromatographed on silica gel eluting with 20% EtOAc/hexane to give 1.58g (54% yield) of 2-ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole, mp, 86-90°C.

Analyses for C₁₇H₁₇NO:

Calculated: C, 81.24; H, 6.82; N, 5.57
Found: C, 81.08; H, 6.92; N, 5.41.

Part D. Preparation of [[2-Ethyl-1-(phenylmethyl)-

-87-

1H-indol-4-yl]oxy]acetic acid methyl ester.

2-ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole (1.56g, 6.2 mmol) was added to a mixture of 248mg (6.2 mmol) of 60% NaH/mineral oil in 20mL DMF and stirred for 0.67 hour.

5

Then 0.6 mL (6.2 mmol) of methyl bromoacetate was added and stirring was continued for 17 hours. The mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate solution was washed with
10 brine, dried (MgSO_4), and concentrated at reduced pressure. The residue was chromatographed on silica gel eluting with 20% EtOAc/hexane, to give 1.37g (69% yield) of [[2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester, 89-92°C.

15 Analyses for $\text{C}_{20}\text{H}_{21}\text{NO}_3$:

Calculated: C, 74.28; H, 6.55; N, 4.33

Found: C, 74.03; H, 6.49; N, 4.60.

Part E. Preparation of [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.

Oxalyl chloride (0.4 mL, 4.2 mmol) was added to 1.36g (4.2 mmol) of [[2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester in 10 mL of methylene
25 chloride and the mixture stirred for 1.5 hours. The mixture was concentrated at reduced pressure and residue taken up in 10 mL of methylene chloride. Anhydrous ammonia was bubbled in for 0.25 hours, the mixture stirred

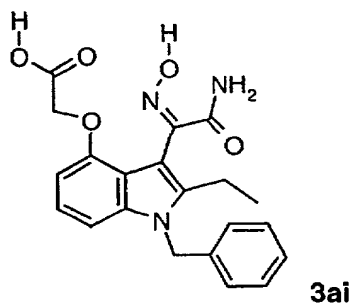
-88-

for 1.5 hours and evaporated at reduced pressure. The residue was stirred with 20 mL of ethyl acetate and the mixture filtered. The filtrate was concentrated to give 1.37g of a mixture of [[3-(2-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester and ammonium chloride. This mixture melted at 172-187°C.

Example 2

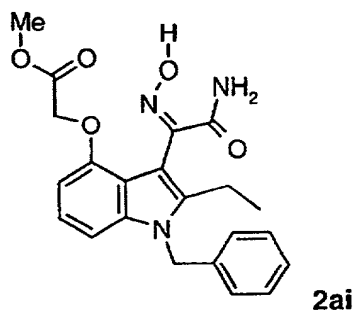
10 (indol-3-oxime amide starting material)

2-[[3-[[2-(Aminooxo)-1-(N-hydroxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid.

**3ai**

A. Preparation of 2-[[3-[[2-(Aminooxo)-1-(N-hydroxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.

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A stirred mixture of **1** (600 mg, 1.52 mmol) and hydroxylamine hydrochloride (528 mg, 7.60 mmol) in THF (4 mL)/CH₃OH (4 mL) was heated at 55 °C for 8 h. After

5 concentration at ambient temperature, the residue was chromatographed on silica (gradient 0-40% EtOAc in CH₂Cl₂) to give the title compound **2ai** (285 mg) as a white solid in 46% yield. IR (CHCl₃) 3510, 3415, 1757, 1667 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.17 (t, *J* = 7.5 Hz, 3H), 2.84

10 (q, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 4.73 (s, 2H), 5.36 (s, 2H), 5.67 (br s, 1H), 6.31 (br s, 1H), 6.41 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.98-7.07 (m, 3H), 7.23-7.32 (m, 3H); ESIMS *m/e* 410 (M⁺+1).

Elemental Analyses for C₂₂H₂₃N₃O₅·0.30(H₂O):

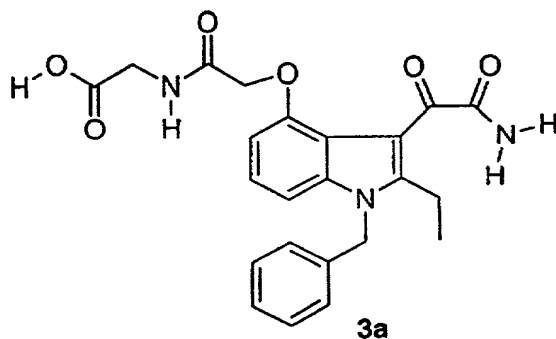
15 Calculated: C, 63.70; H, 5.73; N, 10.13;
 Found: C, 63.68; H, 5.62; N, 10.20.

Example 3

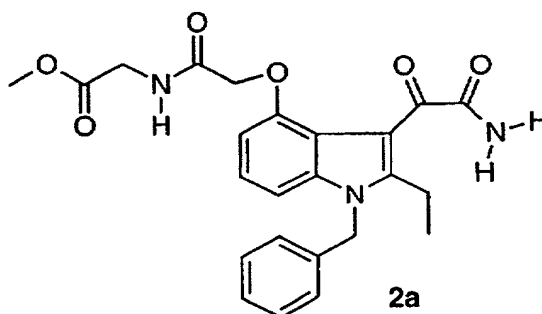
N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-

20 indol-4-yl]oxy]acetyl]glycine

-90-



A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester



5

To a solution of **1** (0.100 g, 0.249 mmol) in 2 mL DMF was added collidine (0.069 mL, 0.523 mmol), methyl glycine hydrochloride (0.0313 g, 0.249 mmol), and benzotriazolyl-*N*-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (0.115 g, 0.261) sequentially at room temperature. After 2.5 hrs. the reaction mixture was concentrated in vacuo to near dryness, then it was taken up in CH₂Cl₂, chromatographed on a silica gel column (gradient 20-40% THF in CH₂Cl₂) and dried in an 80°C vacuum oven to give 0.0768 g of **2a** as a yellow solid in 68% yield. ¹H NMR (DMSO-*d*₆) δ 1.04 (t, *J* = 6.8 Hz, 3H), 2.90 (br q, *J* = 6.8 Hz, 2H),

10

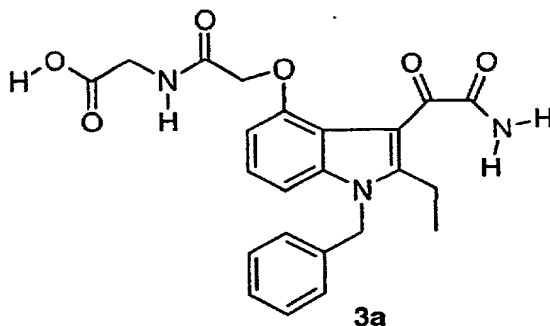
15

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3.57 (s, 3H), 3.88 (d, $J = 5.5$ Hz, 2H), 4.57 (s, 2H), 5.51 (s, 2H), 6.59 (d, $J = 5.6$ Hz, 1H), 7.01-7.08 (m 4H), 7.19-7.30 (m, 3H), 7.55 (s, 1H), 7.99 (s, 1H), 8.40 (t, $J = 5.5$ Hz, 1H).

5

B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine



10 To a solution of 2a (0.035 g, 0.078 mmol) in 1 mL THF, 1 mL MeOH and 0.25 mL distilled H₂O was added 4.17N LiOH (0.093 mL, 0.388 mmol) at room temperature. After 2 hrs. the reaction mixture was acidified with 5N HCl (0.093 mL, 0.465 mmol) and concentrated in vacuo. The residue
15 was taken up in CH₂Cl₂, then rapidly triturated with hexanes to give a yellow suspension which was filtered and dried in an 80°C vacuum oven to give 0.0336 g of 3a as a yellow solid in 99% yield. ¹H NMR (DMSO-d₆) δ 1.04 (t, $J = 5.9$ Hz, 3H), 2.90 (br q, $J = 5.9$ Hz, 2H), 3.80 (d, $J = 4.8$ Hz, 2H), 4.56 (s, 2H), 5.51 (s, 2H), 6.62 (d, $J = 5.8$ Hz, 1H),
20 2H), 4.56 (s, 2H), 5.51 (s, 2H), 6.62 (d, $J = 5.8$ Hz, 1H),

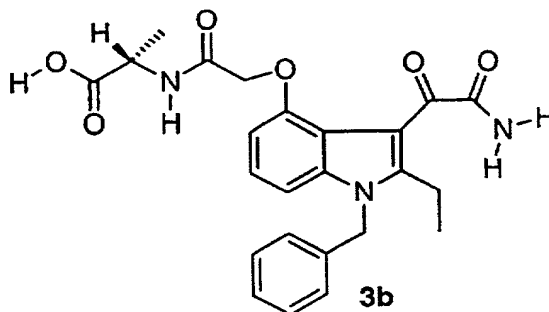
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7.01-7.28 (m, 7H), 7.54 (s, 1H), 7.99 (s, 1H), 8.31 (t, J
= 4.8 Hz, 1H), 12.25-12.75 (br s, 1H).

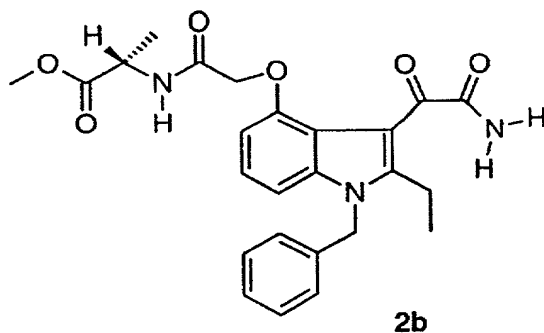
Example 4

- 5 N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-
indol-4-yl]oxy]acetyl]-L-alanine



A. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-
ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine

- 10 methyl ester



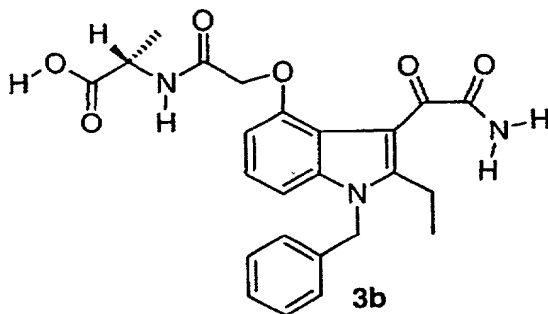
Following the experimental procedure as described for 2a,
2b was obtained as a yellow solid in 65% yield.

- ¹H NMR (DMSO-d₆) δ 1.04 (t, J = 7.2 Hz, 3H), 1.29 (d, J =
15 7.3 Hz, 3H), 2.91 (br q, J = 7.2 Hz, 2H), 3.54 (s, 3H),
4.29 (qd, J = 7.3, 6.8 Hz, 1H), 4.55 (s, 2H), 5.51 (s,

-93-

2H), 6.57 (m, 1H), 6.99 (d, $J = 7.4$ Hz, 2H), 7.07-7.08 (m, 2H), 7.21-7.31 (m, 3H), 7.56 (s, 1H), 8.05 (s, 1H), 8.40 (d, $J = 6.8$ Hz, 1H).

5 **B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine**

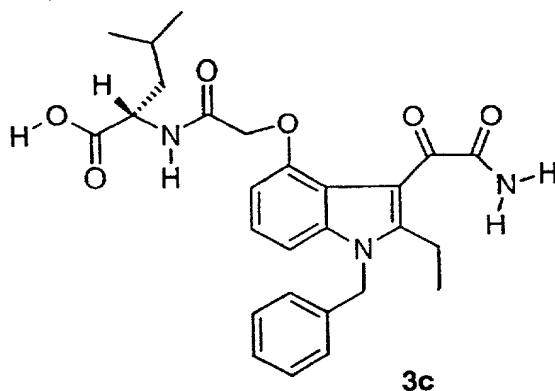


Following the experimental procedure as described for
10 preparing compound 3a, compound 3b, was obtained as a
yellow solid in 89% yield. ^1H NMR (DMSO- d_6) δ 1.04 (t, J
= 7.2 Hz, 3H), 1.29 (d, $J = 7.3$ Hz, 3H), 2.91 (br q, $J =$
7.2 Hz, 2H), 4.22 (td, $J = 7.2, 7.1$ Hz, 1H), 4.54 (s, 2H),
5.51 (s, 2H), 6.60 (d, $J = 6.3$ Hz, 1H), 7.00-7.09 (m, 4H),
15 7.21-7.30 (m, 3H), 7.53 (s, 1H), 8.03 (s, 1H), 8.31 (d, J
= 7.1 Hz, 1H), 12.75-12.84 (br s, 1H).

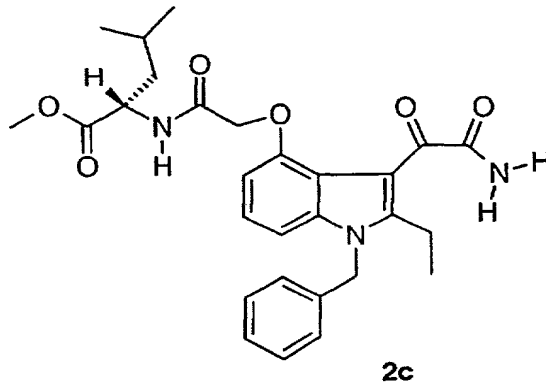
Example 5

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-
20 indol-4-yl]oxy]acetyl]-L-leucine

-94-



A. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester



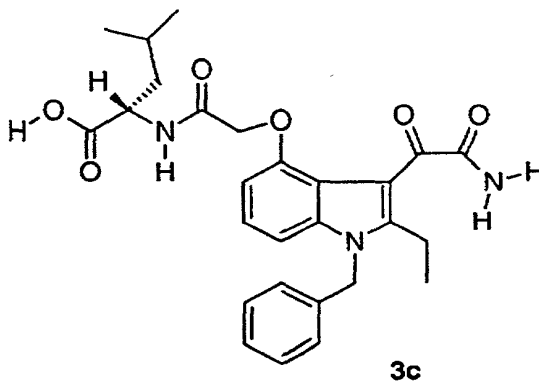
5

Following the experimental procedure as described for 2a, 2c was obtained as a yellow solid in 98% yield. ¹H NMR (DMSO-d₆) δ 0.67 (d, J = 5.5 Hz, 3H), 0.72 (d, J = 5.7 Hz, 3H), 1.05 (t, J = 7.2 Hz, 3H), 1.30-1.50 (m, 2H), 1.51-1.64 (m, 1H), 2.91 (br q, J = 7.2 Hz, 2H), 3.55 (s, 3H), 4.20-4.27 (m, 1H), 4.57 (s, 2H), 5.52 (s, 2H), 6.53-6.56 (m, 1H), 6.97-7.08 (m, 4H), 7.21-7.29 (m, 3H), 7.56 (s, 1H), 8.07 (s, 1H), 8.37 (d, J = 7.3 Hz, 1H).

10

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B. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine



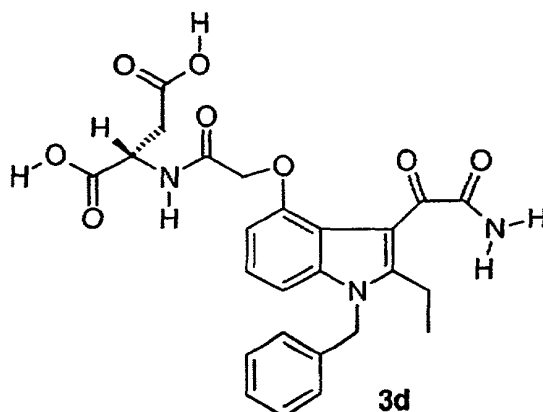
- 5 Following the experimental procedure as described for 3a, 3c was obtained as a yellow solid in 75% yield. ¹H NMR (DMSO-d₆) δ 0.76 (d, J = 5.7 Hz, 3H), 0.78 (d, J = 6.1 Hz, 3H), 1.21 (t, J = 7.3 Hz, 3H), 1.39-1.43 (m, 1H), 1.69 (t, J = 7.3 Hz, 2H), 2.96 (br q, J = 7.3 Hz, 2H), 4.57-4.65 (m, 1H), 4.69 (d, J = 16.0 Hz, 1H), 4.78 (d, J = 16.0 Hz, 1H), 5.38 (s, 2H), 6.59 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.95-7.12 (m, 5H), 7.26-7.32 (m, 3H), 8.17 (d, J = 8.2 Hz, 1H).
- 10

15

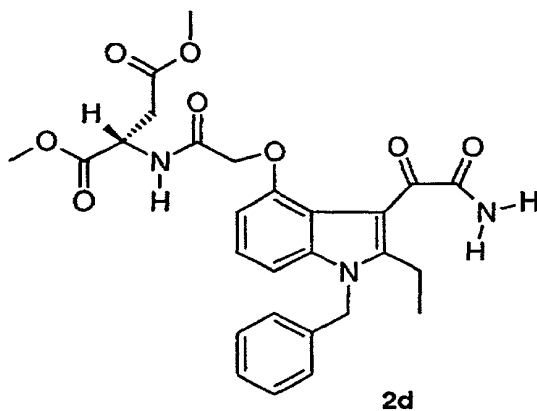
Example 6

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid

-96-



A. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester

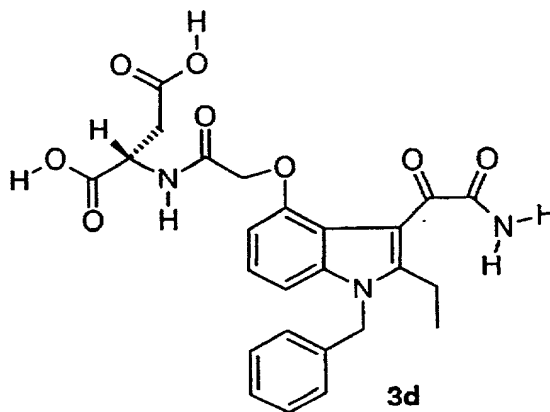


5

Following the experimental procedure as described for 2a, 2d was obtained as a yellow solid in 88% yield. ^1H NMR (DMSO- d_6) δ 1.04 (t, $J = 7.3$ Hz, 3H), 2.72 (dd, $J = 16.6$, 7.1 Hz, 1H), 2.83 (dd, $J = 16.7$, 7.1 Hz, 1H), 2.90 (br q, $J = 7.3$ Hz, 2H), 3.49 (s, 3H), 3.55 (s, 3H), 4.54 (s, 2H), 4.66 (m, 1H), 5.51 (s, 2H), 6.54 (m, 1H), 6.97-7.09 (m, 4H), 7.21-7.30 (m, 3H), 7.50 (s, 1H), 7.97 (s, 1H), 8.52 (d, $J = 7.9$ Hz, 1H).

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B. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid



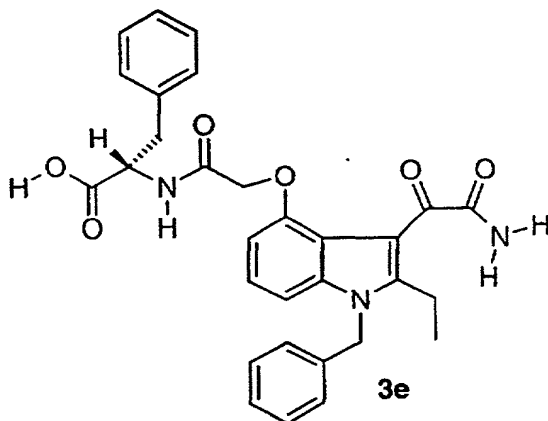
5

Following the experimental procedure as described for 3a, 3d was obtained as a yellow solid in 99% yield. ¹H NMR (DMSO-d₆) δ 1.04 (t, J = 7.2 Hz, 3H), 2.52-2.76 (m, 2H), 2.90 (br q, J = 7.2 Hz, 2H), 4.53 (s, 2H), 4.53-4.60 (m, 1H), 5.50 (s, 2H), 6.59 (d, J = 7.2 Hz, 1H), 6.98-7.09 (m, 4H), 7.19-7.30 (m, 3H), 7.47 (s, 1H), 7.94 (s, 1H), 8.33 (d, J = 7.8 Hz, 1H), 12.40-13.20 (br s, 2H).

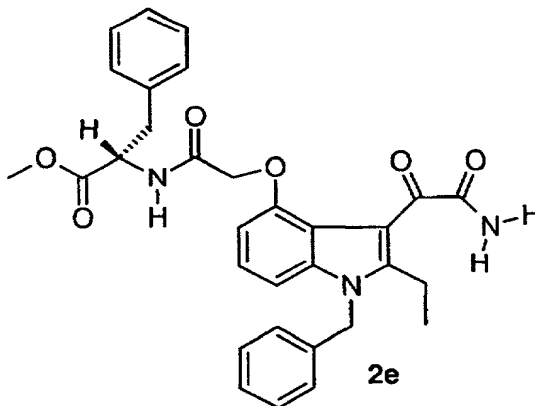
Example 7

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine

-98-



A. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester



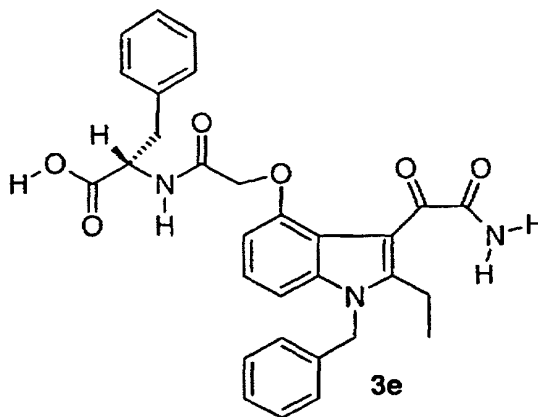
5

Following the experimental procedure as described for 2a, 2e was obtained as a yellow solid in 68% yield. ¹H NMR (DMSO-d₆) δ 1.06 (t, J = 7.2 Hz, 3H), 2.88-3.03 (m, 4H), 3.54 (s, 3H), 4.47-4.50 (m, 1H), 4.50 (s, 2H), 5.52 (s, 2H), 6.41 (d, J = 7.7 Hz, 1H), 6.98-7.11 (m, 9H), 7.21-7.30 (m, 3H), 7.47 (s, 1H), 8.06 (s, 1H), 8.52 (d, J = 7.7 Hz, 1H).

10

-99-

B. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine



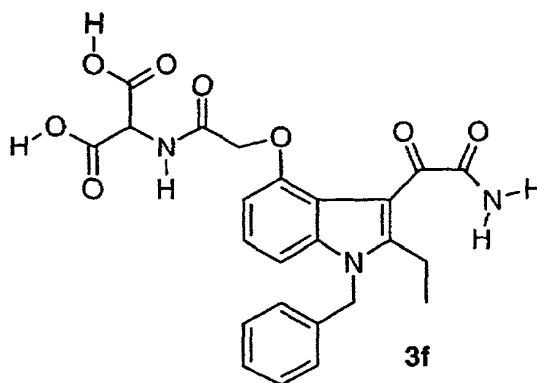
5

Following the experimental procedure as described for 3a, 3e was obtained as a yellow solid in 93% yield. ¹H NMR (DMSO-d₆) δ 1.04 (t, J = 7.1 Hz, 3H), 2.85-3.12 (m, 4H), 4.17-4.26 (m, 1H), 4.54 (s, 2H), 5.51 (s, 2H), 6.59 (d, J = 6.4 Hz, 1H), 6.98-7.09 (m, 9H), 7.19-7.30 (m, 3H), 7.53 (s, 1H), 8.03 (s, 1H), 8.30 (d, J = 7.0 Hz, 1H), 12.50 (br s, 1H).

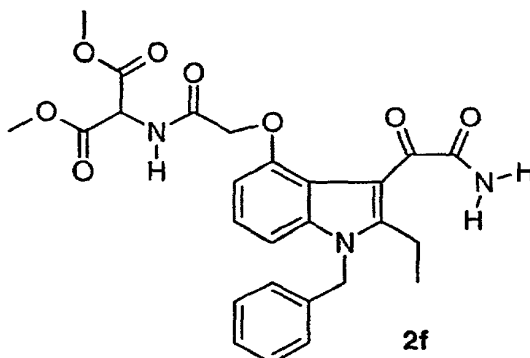
Example 8

15 [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid

-100-



A. Preparation of [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid dimethyl ester

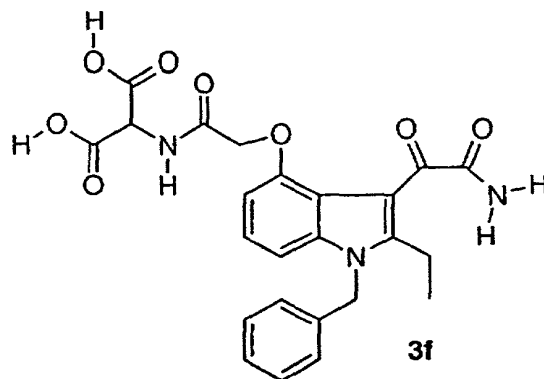


5

Following the experimental procedure as described for 2a, 2f was obtained as a yellow solid in 98% yield. ¹H NMR (DMSO-d₆) δ 1.04 (t, *J* = 7.3 Hz, 3H), 2.90 (br q, *J* = 7.3 Hz, 2H), 3.64 (s, 6H), 4.63 (s, 2H), 5.16 (d, *J* = 7.1 Hz, 1H), 5.51 (s, 2H), 6.54-6.56 (m, 1H), 6.98-7.09 (m, 4H), 7.21-7.30 (m, 3H), 7.43 (s, 1H), 7.88 (s, 1H), 8.90 (d, *J* = 7.2 Hz, 1H).

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B. Preparation of [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid

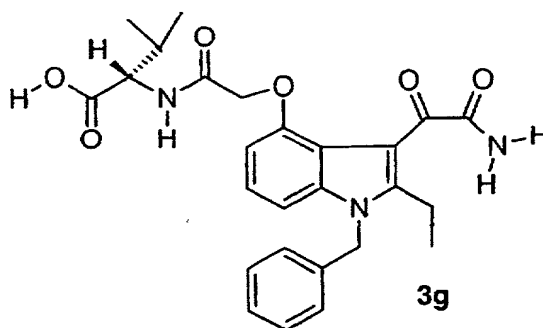


Following the experimental procedure as described for 3a,
5 3f was obtained as a yellow solid in 99% yield. ¹H NMR
(DMSO-d₆) δ 1.04 (t, J = 6.9 Hz, 3H), 2.89 (br q, J = 7.3
Hz, 2H), 4.62 (s, 2H), 4.91 (d, J = 7.2 Hz, 1H), 5.50 (s,
2H), 6.57 (d, J = 7.2 Hz, 1H), 6.98-7.09 (m, 4H), 7.18-
7.30 (m, 3H), 7.37 (s, 1H), 7.83 (s, 1H), 8.55 (d, J = 7.2
10 Hz, 1H), 12.30-13.00 (br s, 2H).

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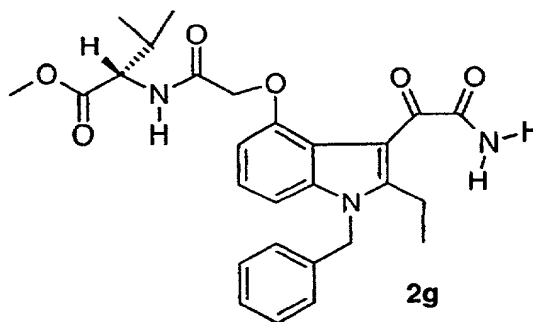
Example 9

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine



5

A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester

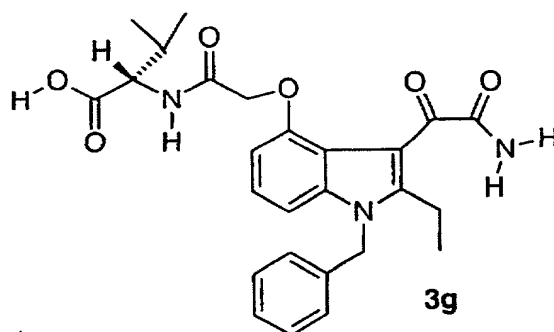


- 10 Following the experimental procedure as described for 2a, 2g was obtained as a yellow solid in 96% yield. ¹H NMR (DMSO-d₆) δ 0.71 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 7.0 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H), 1.99-2.05 (m, 1H), 2.90 (br q, *J* = 7.2 Hz, 2H), 3.54 (s, 3H), 4.11 (br t, *J* = 7.0 Hz, 1H), 4.60 (s, 2H), 5.52 (s, 2H), 6.52 (d, *J* = 4.4 Hz, 1H),
- 15

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6.95 (d, $J = 7.2$ Hz, 2H), 7.06 (br s, 2H), 7.18-7.29 (m, 3H), 7.52 (s, 1H), 8.04 (s, 1H), 8.20 (d, $J = 7.8$ Hz, 1H).

5 B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine

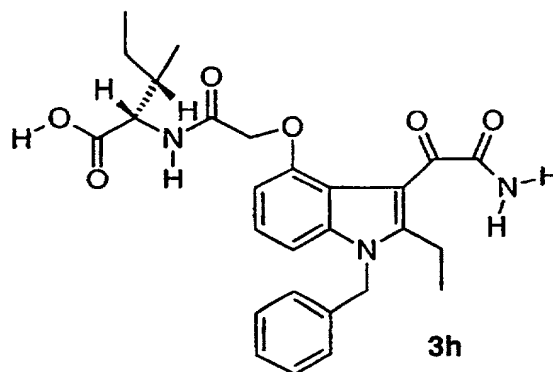


Following the experimental procedure as described for 3a, 3g was obtained as a yellow solid in 94% yield. ^1H NMR (DMSO- d_6) δ 0.71 (d, $J = 6.9$ Hz, 3H), 0.75 (d, $J = 6.8$ Hz, 3H), 1.04 (t, $J = 7.3$ Hz, 3H), 2.01-2.07 (m, 1H), 2.90 (br q, $J = 7.3$ Hz, 2H), 4.09 (br dd, $J = 7.9, 6.2$ Hz, 1H), 4.60 (s, 2H), 5.51 (s, 2H), 6.54 (d, $J = 6.1$ Hz, 1H), 6.95 (d, $J = 7.3$ Hz, 2H), 6.99-7.08 (m, 2H), 7.18-7.29 (m, 3H), 7.49 (s, 1H), 8.01 (s, 1H), 8.08 (d, $J = 8.2$ Hz, 1H), 12.63 (br s, 1H).

-104-

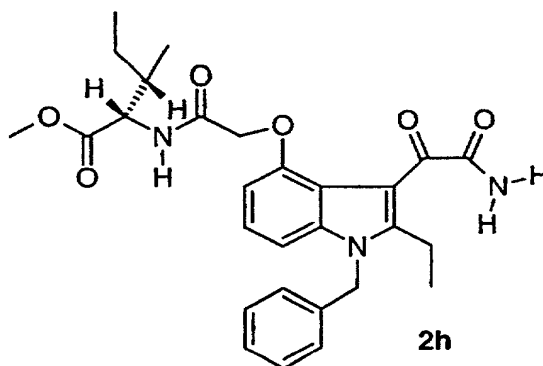
Example 10

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine



5

A. Preparation of N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine methyl ester

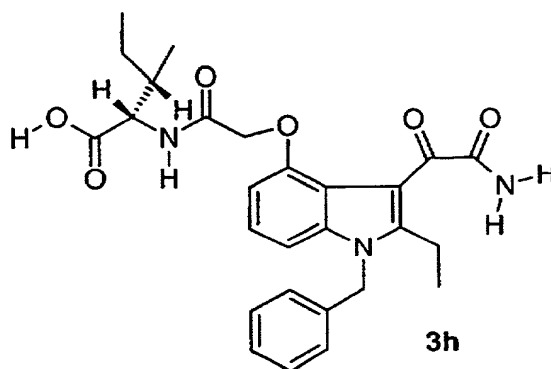


- 10 Following the experimental procedure as described for 2a, 2h was obtained as a yellow solid in 73% yield. ¹H NMR (DMSO-d₆) δ 0.64-0.71 (m, 6H), 0.99-1.08 (m, 4H), 1.21-1.26 (m, 1H), 1.76-1.80 (m, 1H), 2.91 (br q, J = 7.4 Hz, 2H), 3.53 (s, 3H), 4.15 (br t, J = 7.2 Hz, 1H), 4.60 (s,

-105-

2H), 5.52 (s, 2H), 6.52 (m, 1H), 6.96 (d, $J = 7.2$ Hz, 2H),
7.02-7.07 (m, 2H), 7.18-7.29 (m, 3H), 7.53 (s, 1H), 8.04
(s, 1H), 8.23 (d, $J = 7.7$ Hz, 1H).

5 B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine



Following the experimental procedure as described for 3a,
10 3h was obtained as a yellow solid in 92% yield. ^1H NMR
(DMSO- d_6) δ 0.64-0.84 (m, 6H), 1.04 (t, $J = 7.2$ Hz, 3H),
1.21-1.28 (m, 2H), 1.76-1.80 (m, 1H), 2.91 (br q, $J = 7.2$
Hz, 2H), 4.12 (br t, $J = 7.3$ Hz, 1H), 4.59 (s, 2H), 5.51
(s, 2H), 6.55 (d, $J = 6.4$ Hz, 1H), 6.96 (d, $J = 7.2$ Hz,
15 2H), 7.01-7.08 (m, 2H), 7.21-7.29 (m, 3H), 7.51 (s, 1H),
8.01 (s, 1H), 8.11 (d, $J = 7.4$ Hz, 1H), 12.40-12.65 (br s,
1H).

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Assay

The following chromogenic assay procedure was used to identify and evaluate inhibitors of recombinant human secreted phospholipase A₂. The assay described herein

5 has been adapted for high volume screening using 96 well microtiter plates. A general description of this assay method is found in the article, "Analysis of Human Synovial Fluid Phospholipase A₂ on Short Chain Phosphatidylcholine-Mixed Micelles: Development of a

10 Spectrophotometric Assay Suitable for a Microtiterplate Reader", by Laure J. Reynolds, Lori L. Hughes, and Edward A Dennis, Analytical Biochemistry, 204, pp. 190-197, 1992 (the disclosure of which is incorporated herein by reference):

15 Reagents:

REACTION BUFFER -

CaCl₂·2H₂O (1.47 g/L)

KCl (7.455 g/L)

Bovine Serum Albumin (fatty acid free) (1 g/L)

20 (Sigma A-7030, product of Sigma

Chemical Co., St. Louis MO, USA)

TRIS HCl (3.94 g/L)

pH 7.5 (adjust with NaOH)

ENZYME BUFFER -

25 0.05 NaOAc.3H₂O, pH 4.5

0.2 NaCl

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Adjust pH to 4.5 with acetic acid

DTNB - 5,5'-dithiobis-2-nitrobenzoic acid

RACEMIC DIHEPTANOYL THIO - PC

racemic 1,2-bis(heptanoylthio)-1,2-dideoxy-sn-glycero-3-phosphorylcholine

TRITON X-100TM prepare at 6.249 mg/ml in reaction buffer to equal 10uM.

REACTION MIXTURE -

A measured volume of racemic dipheptanoyl thio PC supplied in chloroform at a concentration of 100 mg/ml is taken to dryness and redissolved in 10 millimolar

TRITON X-100TM nonionic detergent aqueous solution. Reaction Buffer is added to the solution, then DTNB to give the Reaction Mixture.

The reaction mixture thus obtained contains 1mM diheptanoly thio-PC substrate, 0.29 mM Triton X-100TM detergent, and 0.12 mM DTMB in a buffered aqueous solution at pH 7.5.

Assay Procedure:

1. Add 0.2 ml reaction mixture to all wells;
2. Add 10 ul test compound (or solvent blank) to appropriate wells, mix 20 seconds;
3. Add 50 nanograms of sPLA₂ (10 microliters) to appropriate wells;

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4. Incubate plate at 40 °C for 30 minutes;
5. Read absorbance of wells at 405 nanometers with an automatic plate reader.

5 All compounds were tested in triplicate.

Typically, compounds were tested at a final concentration of 5 ug/ml. Compounds were considered active when they exhibited 40% inhibition or greater compared to uninhibited control reactions when measured

10 at 405 nanometers. Lack of color development at 405 nanometers evidenced inhibition. Compounds initially found to be active were reassayed to confirm their activity and, if sufficiently active, IC₅₀ values were determined. Typically, the IC₅₀ values (see, Table I,

15 below) were determined by diluting test compound serially two-fold such that the final concentration in the reaction ranged from 45 ug/mL to 0.35 ug/ml. More potent inhibitors required significantly greater dilution. In all cases, % inhibition measured at 405

20 nanometers generated by enzyme reactions containing inhibitors relative to the uninhibited control reactions was determined. Each sample was titrated in triplicate and result values were averaged for plotting and calculation of IC₅₀ values. IC₅₀ were determined by

25 plotting log concentration versus inhibition values in the range from 10-90% inhibition.

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Results of Human Secreted Phospholipase A₂ Inhibition
Tests

Table

Compound No. from Examples 3-10	Inhibition of human secreted PLA ₂ IC ₅₀ ± mean deviation (3-4 tests) (nM)
1	49
2A	529
2B	533
2C	82
2D	874
2E	666
2F	698
2G	283
2H	166
3A	71
3B	59
3C	28
3D	132
3E	64
3F	44.7
3G	36.4
3H	25.1

5 The compound of Example 1 is highly active in
inhibiting sPLA₂.

While the present invention has been illustrated
above by certain specific embodiments, it is not intended
10 that these specific examples should limit the scope of the
invention as described in the appended claims.

13-06-2001

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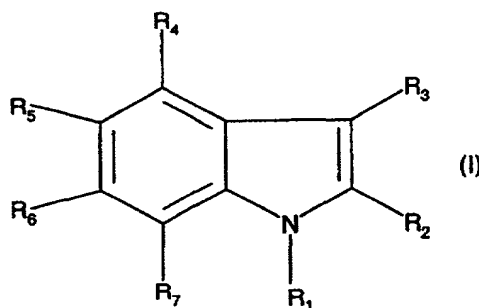
00944673.3(11-07-2000) US00/16319(11-07-2000)

P. CLMSPAMD

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WE CLAIM:

1. An indole compound represented by the formula (I), or a pharmaceutically acceptable salt, solvate, or
5 prodrug derivative thereof;



wherein ;

- 10 R₁ is selected from groups (a), (b), and (c)

wherein;

(a) is C₇-C₂₀ alkyl, C₇-C₂₀ haloalkyl, C₇-C₂₀ alkenyl, C₇-C₂₀ alkynyl, carbocyclic radical, or heterocyclic radical, or

- 15 (b) is a member of (a) substituted with one or more independently selected non-interfering substituents; or

-111-

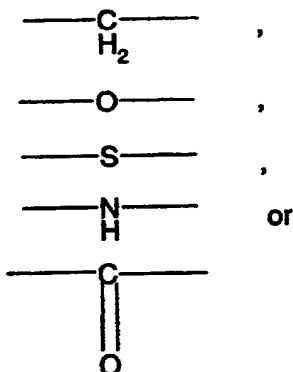
(c) is the group $-(L_1)-R_{11}$; where, $-(L_1)-$ is a divalent linking group of 1 to 8 atoms and where R_{11} is a group selected from (a)

or (b);

- 5 R_2 is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

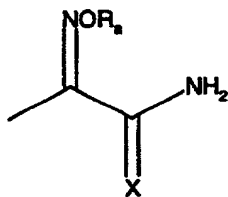
R_3 is $-(L_3)-Z$, where $-(L_3)-$ is a divalent linker group selected from a bond or a divalent group selected from:

10

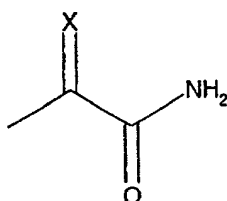


and Z is selected from a group represented by the formulae,

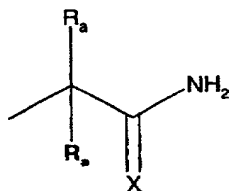
15



-112-



or



wherein, X is oxygen or sulfur; and R_a is selected from hydrogen, C₁-C₈ alkyl, aryl, C₁-C₈ alkaryl, C₁-C₈ alkoxy, aralkyl and -CN;

10 R_4 is the group, $-(L_C)-(acylamino\ acid\ group)$; wherein $-(L_C)-$, is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

15 R_5 is selected from hydrogen, a non-interfering substituent, or the group, $-(L_a)-(acidic\ group)$; wherein $-(L_a)-$, is an acid linker having an acid linker length of 1 to 8;

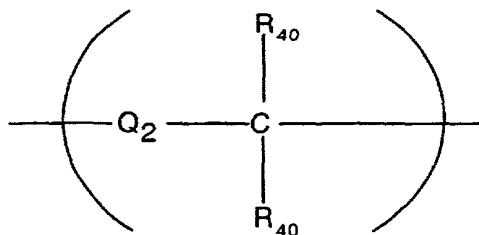
R_6 and R_7 are selected from hydrogen, non-interfering substituent, carbocyclic radical, carbocyclic radical substituted with non-interfering substituent(s),

-113-

heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

2. The compound of claim 1 wherein R₂ is
5 hydrogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, -O-(C₁-C₃ alkyl),
-S-(C₁-C₃ alkyl), C₃-C₄ cycloalkyl, -CF₃, halo, -NO₂, -
CN, or -SO₃.

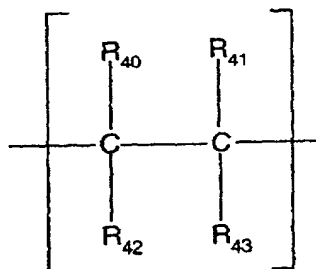
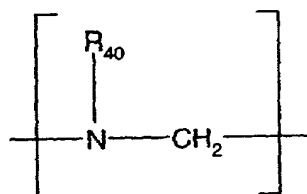
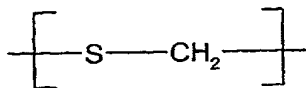
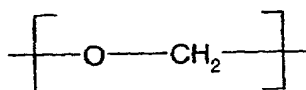
3. The compound of Claim 1 wherein the acylamino
10 acid linker group, -(L_C)-, for R₄ is selected from a
group represented by the formula;



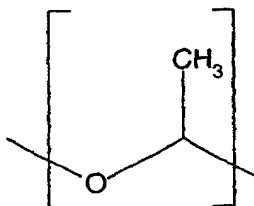
15 where Q₂ is selected from the group -(CH₂)-, -O-, -NH-,
-C(O)-, and -S-, and each R₄₀ is independently selected
from hydrogen, C₁-C₈ alkyl, aryl, C₁-C₈ alkaryl, C₁-C₈
alkoxy, aralkyl, and halo.

20 4. The compound of Claim 1 wherein the acylamino
acid linker group, -(L_C)-, for R₄ selected from -(L_C)-
is a divalent group selected from,

-114-



or

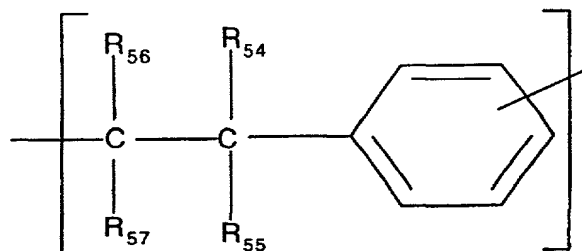
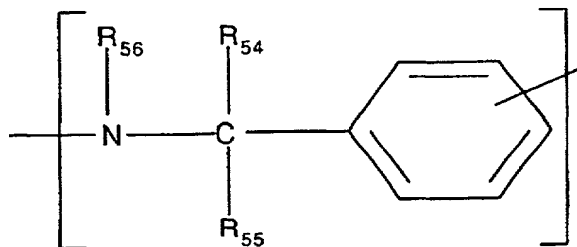
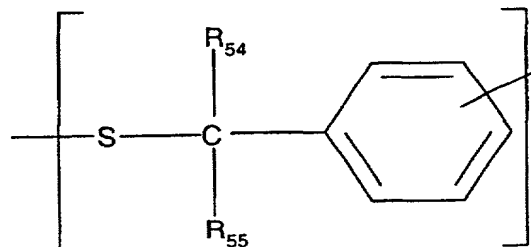
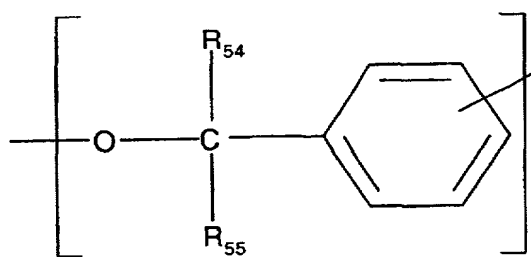


5

where R₄₀, R₄₁, R₄₂, and R₄₃ are each independently selected from hydrogen, C₁-C₈ alkyl.

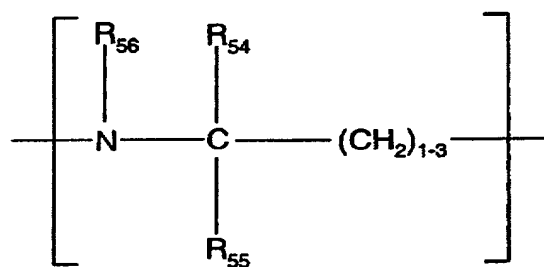
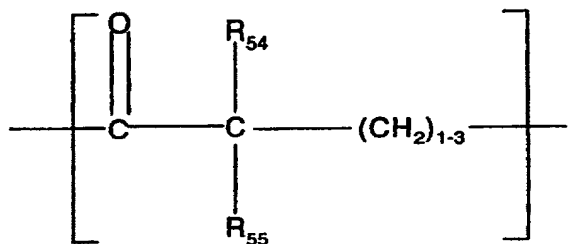
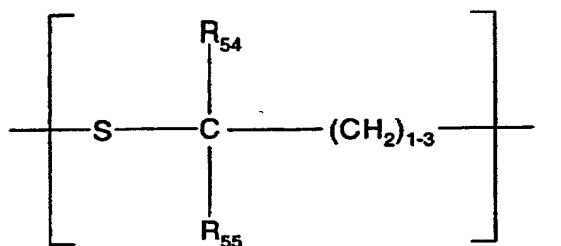
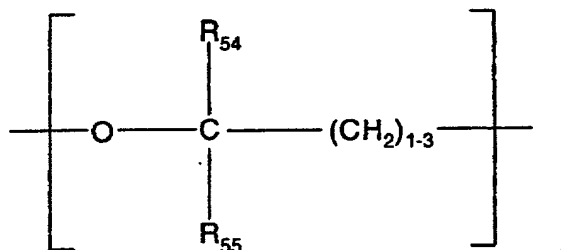
-115-

5. The compound of Claim 1 wherein the acid linker, $-(L_a)-$, for R_5 is selected from a group represented by the formulae consisting of;

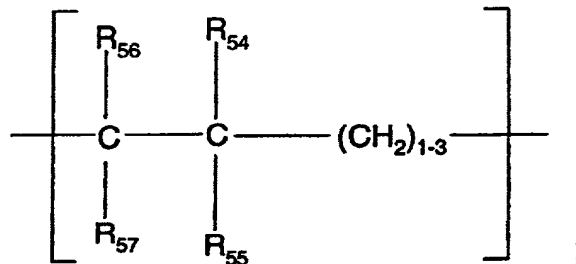


5

-116-



and



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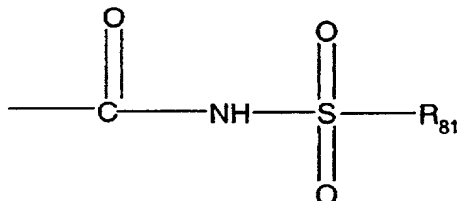
wherein R₅₄, R₅₅, R₅₆ and R₅₇ are each independently hydrogen, C₁-C₈ alkyl, C₁-C₈ haloalkyl, aryl, C₁-C₈ alkoxy, or halo.

- 5 6. The compound of claim 1 wherein R₅ is the group, -(L_a)-(acidic group) and wherein the (acidic group) is selected from the group:

-5-tetrazolyl,

10

-SO₃H,



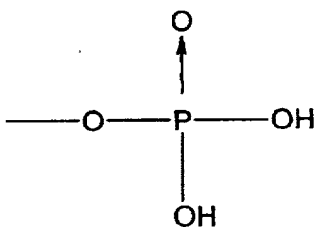
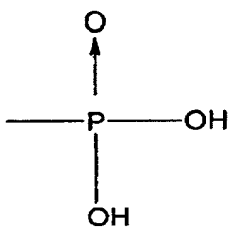
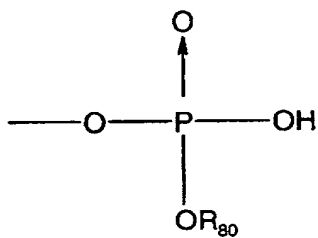
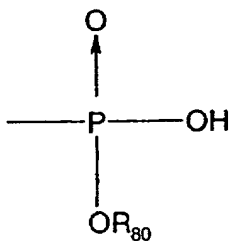
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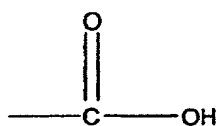
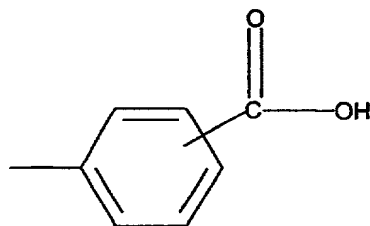
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P. CLMSPAMD

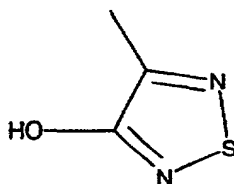
-118-



-119-

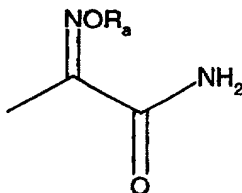


or



where R_{80} is a metal or C_1 - C_8 alkyl and R_{81} is an organic substituent or $-CF_3$.

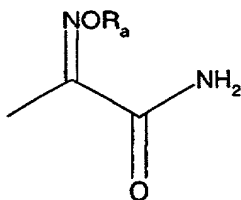
- 5 7. The compound of claim 1 wherein for R_3 , Z is the group represented by the formula;



- and the linking group $-(L_3)-$ is a bond; and R_a is
 10 hydrogen, methyl, ethyl, propyl, isopropyl, phenyl or benzyl.

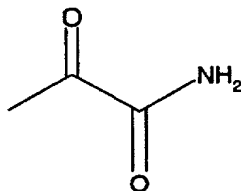
-120-

8. The compound of claim 1 wherein for R_3 , Z is the group represented by the formula;



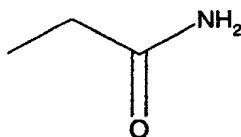
and the linking group $-(L_3)-$ is a bond; and R_a is hydrogen.

9. The compound of claim 1 wherein for R_3 , Z is the group represented by the formula;



10 and the linking group $-(L_3)-$ is a bond.

10. The compound of claim 1 wherein for R_3 , Z is the group represented by the formula;



15 and the linking group $-(L_3)-$ is a bond.

11. The compound of Claim 1 wherein, for R_6 the non-interfering substituent is hydrogen, C_1 - C_8 alkyl,

-121-

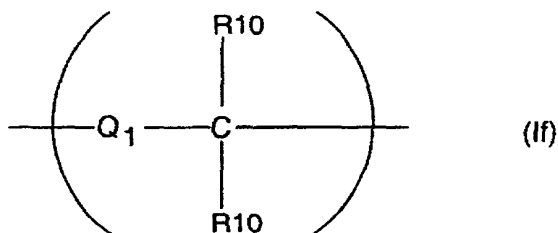
- C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C₁-C₈ alkoxy, C₂-C₈ alkenyloxy, C₂-C₈ alkynyloxy, C₂-C₁₂ alkoxyalkyl, C₂-C₁₂ alkoxyalkyloxy, C₂-C₁₂ alkylcarbonyl, C₂-C₁₂ alkylcarbonylamino, C₂-C₁₂ alkoxyamino, C₂-C₁₂ alkoxyaminocarbonyl, C₁-C₁₂ alkylamino, C₁-C₆ alkylthio, C₂-C₁₂ alkylthiocarbonyl, C₁-C₈ alkylsulfinyl, C₁-C₈ alkylsulfonyl, C₂-C₈ haloalkoxy, C₁-C₈ haloalkylsulfonyl, C₂-C₈ haloalkyl, C₁-C₈ hydroxyalkyl, -C(O)O(C₁-C₈ alkyl), -(CH₂)_n-O-(C₁-C₈ alkyl), benzyloxy, phenoxy, phenylthio, -(CONHSO₂R), -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -(CH₂)_n-CO₂H, chloro, cyano, cyanoguanidiny, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, -SO₃H, thioacetal, thiocarbonyl, or carbonyl; where n is from 1 to 8.

12. The compound of Claim 1 wherein for R₁ the divalent linking group -(L₁)- is selected from a group represented by the formulae (Ia), (Ib), (Ic), (Id), (Ie), and (If):

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or

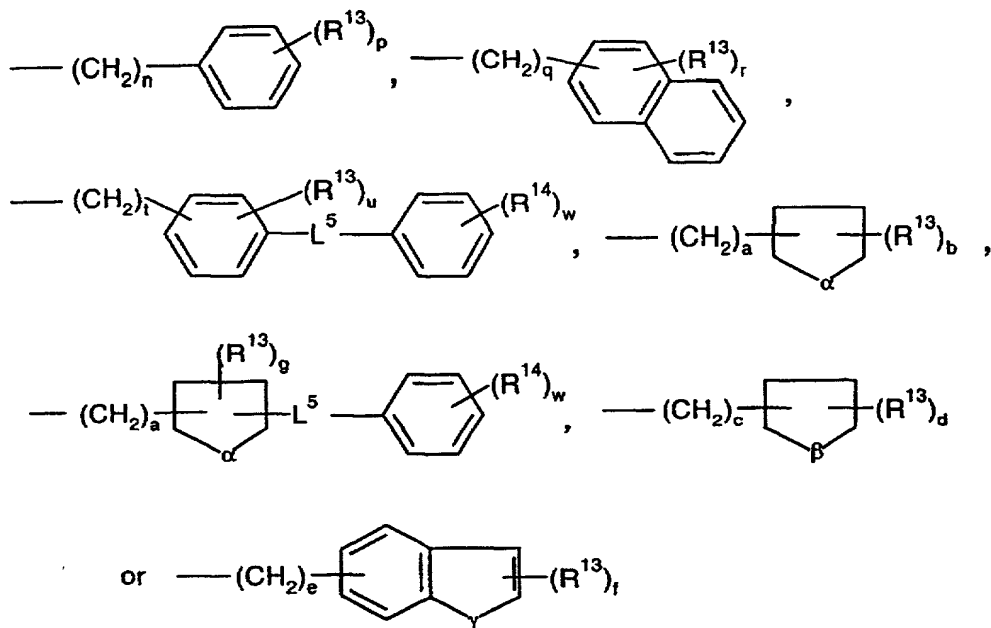


- 5 where Q_1 is a bond or any of the divalent groups Ia, Ib, Ic, Id, and Ie and R_{10} is independently -H, C_{1-8} alkyl, C_{1-8} haloalkyl or C_{1-8} alkoxy.

13. The compound of claim 1 wherein the linking group $-(L_1)-$ of R_1 is $-(CH_2)-$ or $-(CH_2-CH_2)-$.

14. The compound of claim 1 wherein the linking group $-(L_{11})-$ of R_{11} is a bond and R_{11} is $-(CH_2)_m-R^{12}$ wherein m is an integer from 1 to 6, and R^{12} is a group
- 15 represented by the formula:

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wherein a, c, e, n, q, and t are independently an integer from 0 to 2, R^{13} and R^{14} are independently selected from a halogen, C_1 to C_8 alkyl, C_1 to C_8

5 alkyloxy, C_1 to C_8 alkylthio, aryl, heteroaryl, and C_1 to C_8 haloalkyl, α is an oxygen atom or a sulfur atom, L^5 is a bond, $-(CH_2)_v-$,

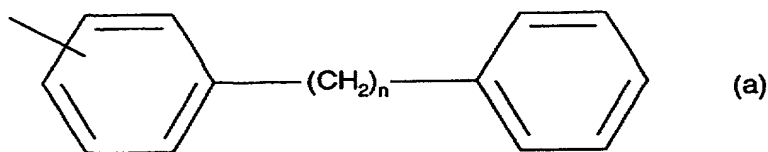
$-C=C-$, $-CC-$, $-O-$, or $-S-$, v is an integer from 0 to 2, β is $-CH_2-$ or $-(CH_2)_2-$, γ is an oxygen atom or a sulfur

10 atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group

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consisting of C₁ to C₆ alkyl, C₁ to C₈ alkyloxy, C₁ to C₈ haloalkyloxy, C₁ to C₈ haloalkyl, aryl, and a halogen..

15. The compound of claim 1 wherein for R₁ the
5 group R₁₁ is a substituted or unsubstituted carbocyclic radical selected from the group consisting of cycloalkyl, cycloalkenyl, phenyl, spiro[5.5]undecanyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xlenyl, indenyl, stilbenyl, terphenyl,
10 diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzylyl and related bibenzylyl homologues represented by the formula (a):

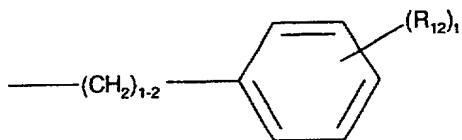


where n is a number from 1 to 8.

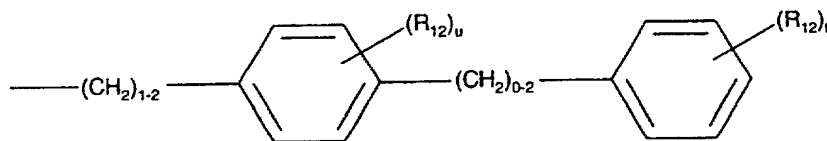
15

16. The compound of Claim 12 wherein for R₁ the combined group -(L₁)-R₁₁ is selected from the groups;

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or



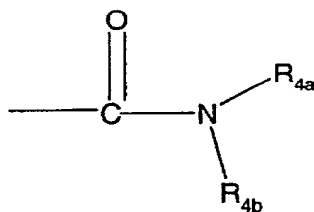
where R_{12} is a radical independently selected from halo, C_1 - C_{10} alkyl, C_1 - C_{10} alkoxy, $-S-(C_1-C_{10})$ alkyl, and C_1 -
 5 C_{10} haloalkyl, C_1 - C_{10} hydroxyalkyl and t is a number from 0 to 5 and u is a number from 0 to 4.

17. The compound of claim 1 wherein for R_1 the radical R_{11} is a substituted or unsubstituted
 10 heterocyclic radical selected from pyrrolyl, pyrrolodiny, piperidiny, furanyl, thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, indolyl, carbazolyl, norharmanyl, azaindolyl, benzofuranyl,
 15 dibenzofuranyl, dibenzothiophenyl, indazolyl, imidazo(1,2-A)pyridinyl, benzotriazolyl, anthranilyl, 1,2-benzisoxazolyl, benzoxazolyl, benzothiazolyl, purinyl, pyridinyl, dipyridyl, phenylpyridinyl, benzylpyridinyl, pyrimidinyl, phenylpyrimidinyl,
 20 pyrazinyl, 1,3,5-triazinyl, quinolinyl, phthalazinyl,

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quinazolinylmorpholino, thiomorpholino, homopiperazinyl,
 tetrahydrofuranyl, tetrahydropyranyl, oxacanyl, 1,3-
 dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl,
 tetrahydrothiopheneyl, pentamethylenesulfadyl, 1,3-
 5 dithianyl, 1,4-dithianyl, 1,4-thioxanyl, azetidiny,
 hexamethyleneiminium, heptamethyleneiminium, piperazinyl
 or quinoxaliny.

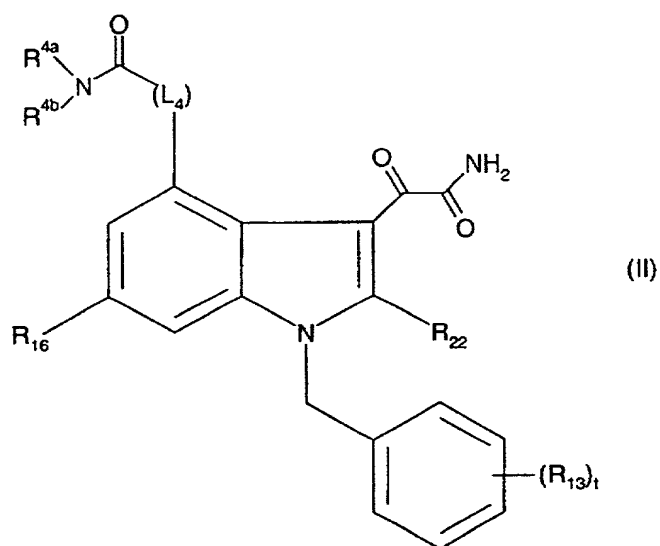
18. The compound of claim 1 wherein R₄ is the
 10 group, -(L_C)-(acylamino acid group) and wherein the
 (acylamino acid group) is:



15 and R^{4a} is selected from the group consisting of H, (C₁-
 C₆)alkyl, (C₁-C₆)alkoxy, heteroaryl and aryl; and wherein
 NR^{4b} is an amino acid residue with the nitrogen atom being
 part of the amino group of the amino acid.

20 19. An indole compound represented by the
 formula (II), or a pharmaceutically acceptable salt,
 solvate, or prodrug derivative thereof;

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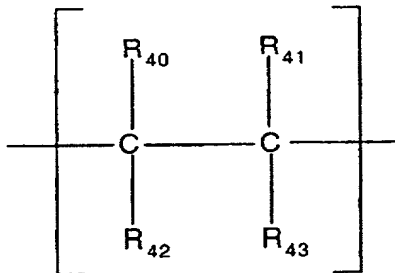
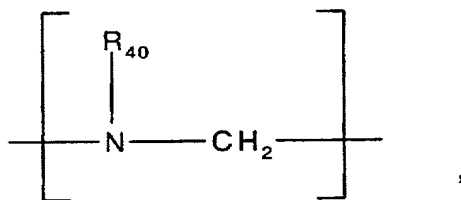
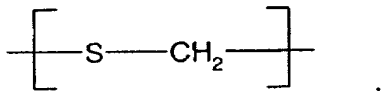
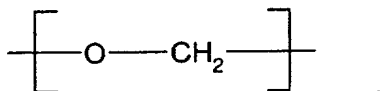
5 wherein ;

R_{22} is selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, -CF₃, -Cl, -Br, or -O-CH₃;

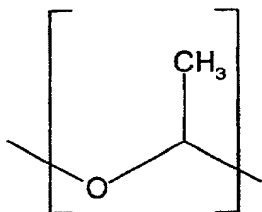
R^{4a} is hydrogen; and

10 NR^{4b} is an amino acid residue with the nitrogen atom being part of the amino group of the amino acid, and -
(L_C)- is a divalent group selected from;

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or



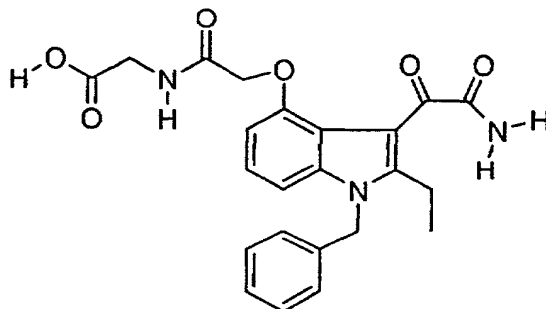
- 5 where R₄₀, R₄₁, R₄₂, and R₄₃ are each independently selected from hydrogen or C₁-C₈ alkyl.

R₁₆ is selected from hydrogen, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio C₁-C₈ haloalkyl, C₁-C₈ hydroxyalkyl, and halo.

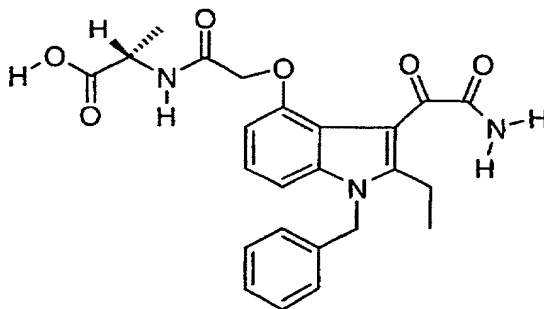
10

5

20. An indole compound represented by the formulae (C1), (C2), (C3), (C4), (C5), (C6), (C7), (C8), (C9), (C10) or (C11);



(C1),



(C2) ,

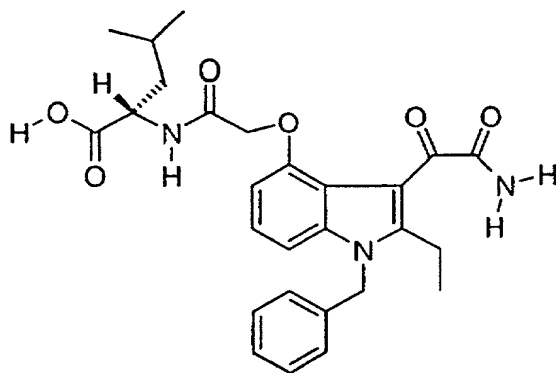
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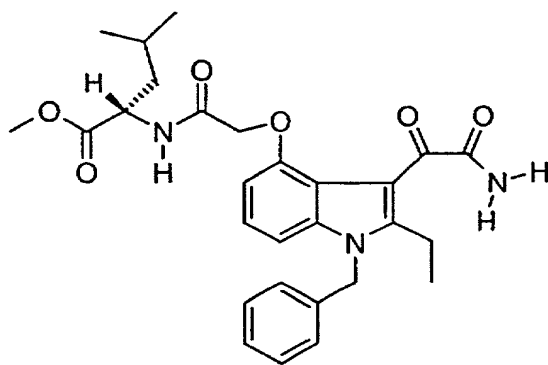
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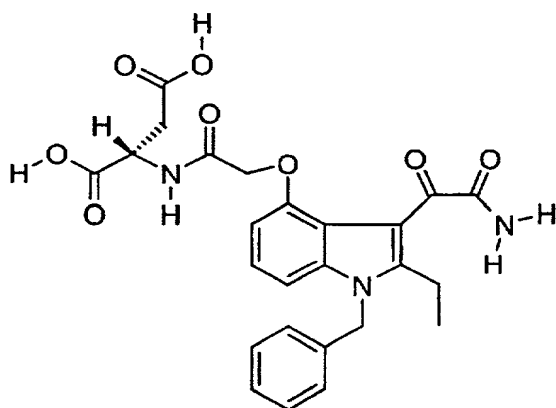
-130-



(C3),



(C4),



(C5),

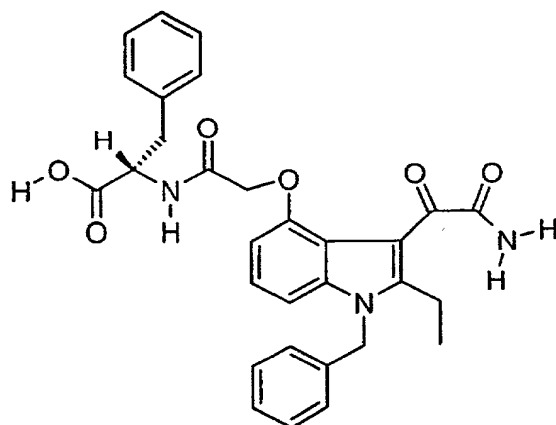
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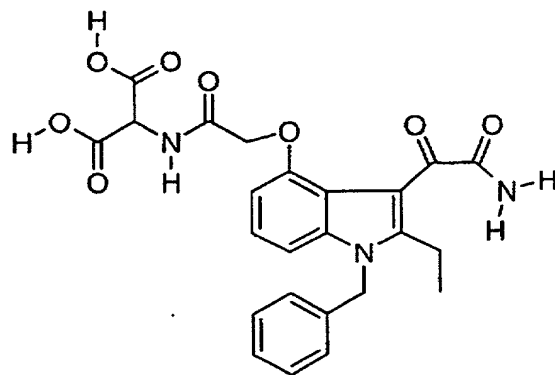
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P CLMSPAMD

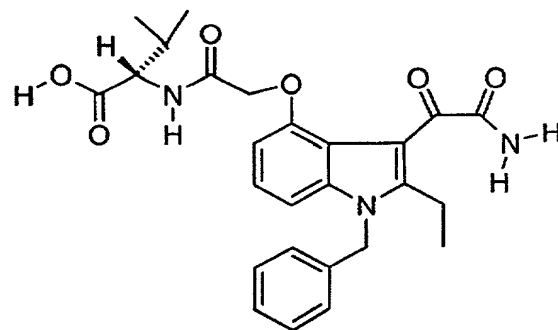
-131-



(C6),



(C7),



(C8),

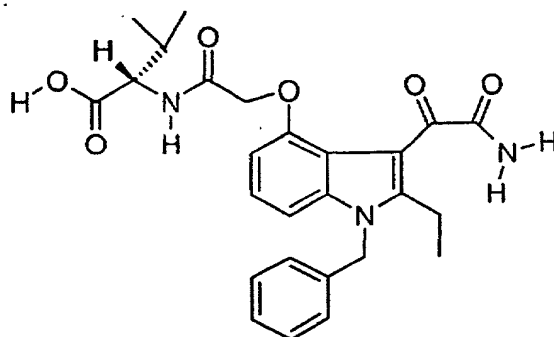
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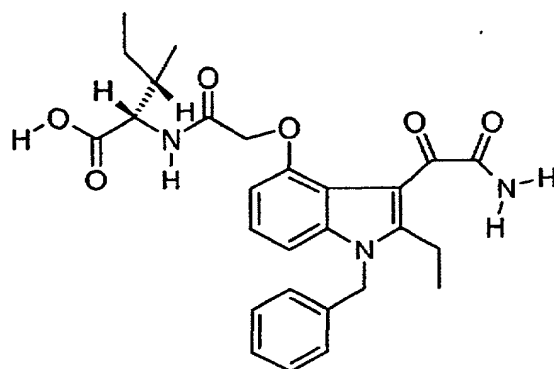
00944673 3 (11-07-2000) US0016319 (11-07-2000)

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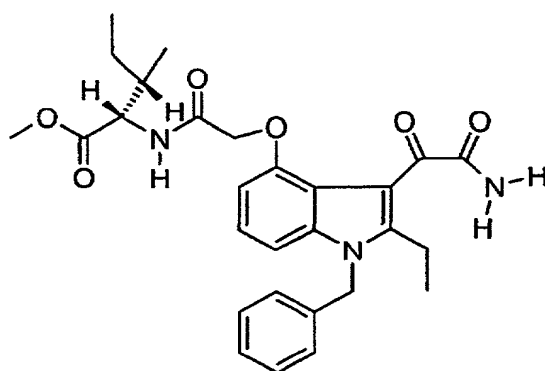
-132-



(C9),



(C10) and



(C11)

or pharmaceutically acceptable salts or prodrugs thereof.

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20. A compound of claim 1 selected from the group consisting of:

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine ;

5 N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine;

10 N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine;

15 N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester;

20 N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

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N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

5 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester;

10 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-
indol-4-yl]oxy]acetamido]malonic acid;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-
indol-4-yl]oxy]acetamido]malonic acid dimethyl ester

15 [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-
indol-4-yl]oxy]acetamido]malonic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-valine;

20 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-valine;

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N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-isoleucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-isoleucine methyl ester; and

5 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-isoleucine.

21. A pharmaceutical formulation comprising a indole
compound as claimed in claim 1 together with a
10 pharmaceutically acceptable carrier or diluent therefor.

22. A method of inhibiting sPLA₂ mediated release
of fatty acid which comprises contacting sPLA₂ with a
therapeutically effective amount of indole compound as
15 claimed in claim 1.

23. A method of treating a mammal, including a
human, to alleviate the pathological effects of
Inflammatory Diseases; wherein the method comprises
20 administration to said mammal of at least one indole
compound as claimed in Claim 1 in a pharmaceutically
effective amount.

24. A compound of claim 1 or a pharmaceutical
25 formulation containing an effective amount of the

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compound of claim 1 in treatment of Inflammatory Diseases.

25. A compound of claim 1 or a pharmaceutical
5 formulation containing an effective amount of the
compound of claim 1 for use as an inhibitor for
inhibiting sPLA₂ mediated release of fatty acid.

26. Use of a pharmaceutical composition comprising
10 sPLA₂ inhibitor compounds according to Claim 1 and
mixtures thereof for the manufacture of a medicament for
the therapeutic treatment of Inflammatory Diseases.

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+

PTO/SB/01 (8-96) (MODIFIED)

Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

☒ Declaration Submitted with Initial Filing
☐ Declaration Submitted after Initial Filing

Attorney Docket Number	X-12420
First Named Inventor	Ho-Shen Lin
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

sPLA₂ INHIBITORS

the specification of which
☐ is attached hereto
OR

☒ was filed on 11 July 2000 as United States Application Number or PCT International (MM/DD/YYYY)

Application Number PCT/US00/16319 and was amended on 11 June 2001 (if applicable) (MM/DD/YYYY)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached	
				YES	NO
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional applications(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	<input type="checkbox"/> Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.
60/144,502	19 July 1999	

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PTO/SB/01 (8-96) (MODIFIED)

Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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Aleen Palmberg	40,422
Thomas G. Plant	35,784
Edward Prein	37,212
Grant E. Reed	41,264
James J. Sales	33,773
Michael J. Sayles	32,295
Robert L. Sharp	45,609
David M. Stermerick	40,187
Mark J. Stewart	43,936
Robert D. Titus	40,206
Robert C. Tucker	45,165
Tina M. Tucker	47,145
MaCharri Vomdran-Jones	36,711
Gilbert T. Voy	43,972
Thomas D. Webster	39,872
Lawrence T. Welch	29,487
Alexander Wilson	45,782
Dan L. Wood	48,613

☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

Direct all correspondence to:

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Country Telephone **(317) 276-9477** Fax **(317) 276-3861**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A Petition has been filed for this unsigned inventor

Given Name **Ho-Shen** Middle Name **Lin** Family Name **Lin** Suffix **e.g. Jr.**
Inventor's Signature *Ho-Shen Lin* Date **12-05-2000**
Residence: City **Indianapolis** State **IN** Country **USA** Citizenship **USA**
Address **8128 Trevellian Way**
Post Office Address **SAME AS ABOVE**

City **Indianapolis** State **IN** Zip **46217** Country **USA**

☒ Additional Inventors are being named on supplement sheet(s) attached hereto.

Please type a plus sign (+) inside this box

+

PTO/SB/01 (8-96) (MODIFIED)

Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

Name of Additional Joint Inventor, if any:				<input type="checkbox"/> A Petition has been filed for this unsigned inventor			
Given Name	Michael	Middle Name	Enrico	Family Name	Richett	Suffix e.g. Jr.	
Inventor's Signature	<i>Michael Enrico Richett</i>					Date	12-5-2009
Residence: City	Indianapolis	State	IN	Country	USA	Citizenship	USA
Address	5832 Baron Court <i>IN</i>						
Post Office Address	SAME AS ABOVE						
City	Indianapolis	State	IN	Zip	46250	Country	USA

Name of Additional Joint Inventor, if any:				<input type="checkbox"/> A Petition has been filed for this unsigned inventor			
Given Name		Middle Name		Family Name		Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address	SAME AS ABOVE						
City		State		Zip		Country	

Name of Additional Joint Inventor, if any:				<input type="checkbox"/> A Petition has been filed for this unsigned inventor			
Given Name		Middle Name		Family Name		Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City		State		Country	Spain	Citizenship	Spain
Post Office Address							
Post Office Address	SAME AS ABOVE						
City		State		Zip		Country	Spain

Name of Additional Joint Inventor, if any:				<input type="checkbox"/> A Petition has been filed for this unsigned inventor			
Given Name		Middle Name		Family Name		Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address	SAME AS ABOVE						
City		State		Zip		Country	